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TUBERCULOUS TRACHEOBRONCHITIS

ROENTGEN PATHOLOGY*

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THE detection of evidence of complications of pulmonary tuberculosis is one of the responsibilities of the roentgenologist. During the past few years attention has again been called to the frequency and the clinical and bronchoscopic manifestations of tuberculous involvement of the tracheal and bronchial mucosa. As a sequel to several reports[3,4,6] from the University of Michigan Hospital, the roentgenologic findings in the cases finally classified as tuberculous tracheobronchitis during the past five years have been surveyed. An attempt has been made to determine whether or not there is a constant roentgenographic pattern. A selected group of 40 cases has been subjected to a detailed analysis. Six are presented here as illustrative examples.

The clinical syndrome has been described in the previous papers as presenting the symptoms of respiratory wheeze or rattle, often noted by the patient; attacks of asthmatoid breathing with some sensation of substernal constriction; paroxysms of violent coughing and choking with unusual difficulty in raising sputum. Parasternal rhonchi (especially in the stenotic lesions), dyspnea, and a constant low grade of cyanosis or intermittent cyanosis, in spite of a vital capacity of 1,200 cc. or more, may dominate the physical signs. Gradual or sudden onset of severe obstructive episodes with physical signs of atelectasis in some degree, elevation of the diaphragm and mediastinal shift are observed. For the apparent extent of the disease, the sputum is often excessive in amount, or disproportionate in number of bacilli, variable in quantity, exceptionally tenacious and difficult to evacuate. The character of the sputum or bacterial count may shift sharply with collapse therapy.

Bronchoscopically, four general groups have been described: (1) a non-ulcerative and non-stenotic involvement with edema, congestion and granularity of the mucosa with submucosal infiltration and varying numbers of epithelioid tubercles; (2) hyper-

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plastic changes in the mucous membrane with the formation of tuberculomata; (3) ulcerative, and (4) fibrostenotic.

The pathogenesis has been carefully studied by Bugher, *et al.*, who found an incidence of 41 per cent in 122 autopsies of patients dying of pulmonary tuberculosis. The complication is relatively uncommon in patients with miliary tuberculosis, but approaches a frequency of 50 per cent in the non-miliary group. With exception of the occasional ulceration of a tuberculous gland through the bronchial wall, or the infiltration of a bronchus directly from surrounding tuberculous lung tissue, both bronchial and tracheal lesions would appear to be consistently implantation or contact infection. Mucin formation is increased, the mucous glands enlarged. Small epithelioid tubercles with caseating centers appear more commonly on the posterior or posterolateral walls of the bronchi and trachea. Small ulcers are usually associated with subjacent tubercles, and there is a tendency to submucosal extension laterally. Diffuse chronic inflammation with edema and fibrosis is associated with a marked degree of thickening of the submucosa and consequent reduction in the lumen of the bronchus or trachea. This submucosal infiltration may account for the sign, recently described by Oechsli as a thickening along the bronchovascular trunk leading from the parenchymal lesion to the root of the lung, with accented visibility of the bronchial lumen.

Collapse therapy in these patients has not been as satisfactory as in patients without this complication, and in some has seemed to aggravate the symptoms and signs. Roentgen therapy has been tried but with little or no improvement.

The 40 cases selected for this analysis had had either positive bronchoscopic confirmation of the diagnosis (33 cases, or 82.5 per cent), or the clinical and roentgenologic syndrome was sufficiently characteristic to warrant a diagnosis of tuberculous tracheobronchitis.

Predominant symptoms and signs were:

Persistent cough	34 cases	Rhonchi	7 cases
Wheezing	19 cases	Cyanosis	4 cases
Dyspnea	12 cases		

Positive sputum disproportionate to roentgenographic evidence of activity or extent of disease — 14 cases

Progressive decrease in vital capacity not attributable to any collapse measures — 6 cases

Increase in symptoms with collapse therapy (16 patients) — 7 cases

Cough occurred as the only symptom in 11 (with rhonchi in 2); cough and dyspnea were present in 2; cough and wheezing in 8; cough, wheezing and dyspnea in 8; cough, wheezing and cyanosis in 1; cough, wheezing, dyspnea and cyanosis in 4.

The frequency of various roentgenographic changes as related to symptoms is shown in Table 1.

It is evident that atelectasis (roentgenographically, a relatively uniform increase in density of an anatomic segment, lobule, lobe or lung with decrease in volume, indicating the degree of airlessness, as distinguished from the density of consolidation in which no loss of volume occurs) is the most common change. Upon institution of some method of collapse therapy, a degree of collapse greater than would be expected from the previous roentgenographic extent of disease was next most frequent. Visible changes in the bronchial lumen parallel the latter. An important roentgen sign is the relative minimal evidence of pulmonary pathology in the presence of clinical symptoms and signs of considerable disease. Although acid-fact organisms other than the tubercle bacillus may appear in the sputum, the persistence of "positive sputum" with other signs of the disease in the face of a definitely minor parenchymal lesion or regressive one (on chest films) should arouse suspicion of such a complication.

The nature of the excavation seems to be of some importance. The non-obstructed tuberculous cavity without gross infiltration of the surrounding lung will show a loss of transverse diameter or uniform change in diameters upon institution of a pneumothorax. If, however, the cavity maintains

its volume and a spherical contour in the presence of satisfactory collapse of the surrounding lung, and particularly if it should seem to increase in diameter, obstruction of its bronchus may be suspected. This has been called the "tension" or "tennis ball" cavity.

Table I

Roentgenographic changes	Clinical symptoms							
	Rhonchi	Cough only	Cough and Dyspnea	Cough and Wheeze	Cough, Wheeze and Dyspnea	Cough, Wheeze and Cyanosis	Cough, Wheeze, Dyspnea and Cyanosis	Total Frequency
Atelectasis	6	13	1	6	6	1	3	30
Spontaneous intermittent atelectasis	2	1	1	1	2	0	0	5
Extent of roentgen pathology not compatible with clinical course	6	4	0	2	2	0	2	10
Degree of collapse greater than expected from evident lesion	3	3	2	5	2	0	1	13
Sudden increased atelectasis with collapse therapy	0	0	0	2	1	0	1	4
Visible changes in bronchi	5(1b)	6(2b)	0	3	2(1b)	2(1b)	0	13
Oechsli sign	2	2	0	2	1	0	0	5
"Tennis ball" cavity		1		1				2

(1b) indicates number of patients having had bronchograms.

In illustration we present the following cases from this series:

I. Minor roentgenologic evidence of pulmonary tuberculosis with persistent positive sputum rhonchi, wheeze and dyspnea.

Case 1. G. B., female, aged thirty-seven, No. 366737 (Barnwell, Littig and Culp's Case 6). "Influenza," January, 1935, with cough and fever to 102° F. Cough persisted, slightly productive. Tubercle bacilli were reported by her referring physician in May, 1935, although chest roentgenogram was said to have shown no lesion. Huskiness of voice, shortness of breath and "rattles" in the chest had been noted for a month before admission (August, 1935).

Roentgenogram, August 14, 1935 (Fig. 1*a*): Minimal pulmonary tuberculosis, left apex.

Physical examination on admission revealed palpable rhonchi over the left chest, with wheezes and râles, the last being coarse in the axilla and base; sputum 40–50 gm. daily (excessive for extent of apparent lesion), positive; vital capacity 1,800 cc.

Bronchoscopy (Dr. Samson), August 30, 1935: Active ulcerative tuberculous tracheobronchitis with slight stenosis of the left bronchus at its orifice.

Roentgenograms: September 17, 1935 (Fig. 1*b*): parenchymal infiltration (possibly an early lesion) appeared in the left mid-axilla, 3rd–5th ribs, as well as the former lesion in the 1st interspace, anteriorly. October 18, 1935 (Fig. 1*c*): mediastinal shift to the left, parenchymal lesion not changed. This suggested an early obstruction of the bronchus. November 11, 1935 (Fig. 1*d*): gross atelectasis of left lung. The patient had described a left pleuritic pain, three days previously. Sputum 30 gm. daily, positive.

Comment. This case demonstrates the rapid changes which may occur, although upon the initial examination a relatively minor lesion was in evidence. Roentgen therapy had been administered in September and again on November 7. It probably had little to do with the changes observed.

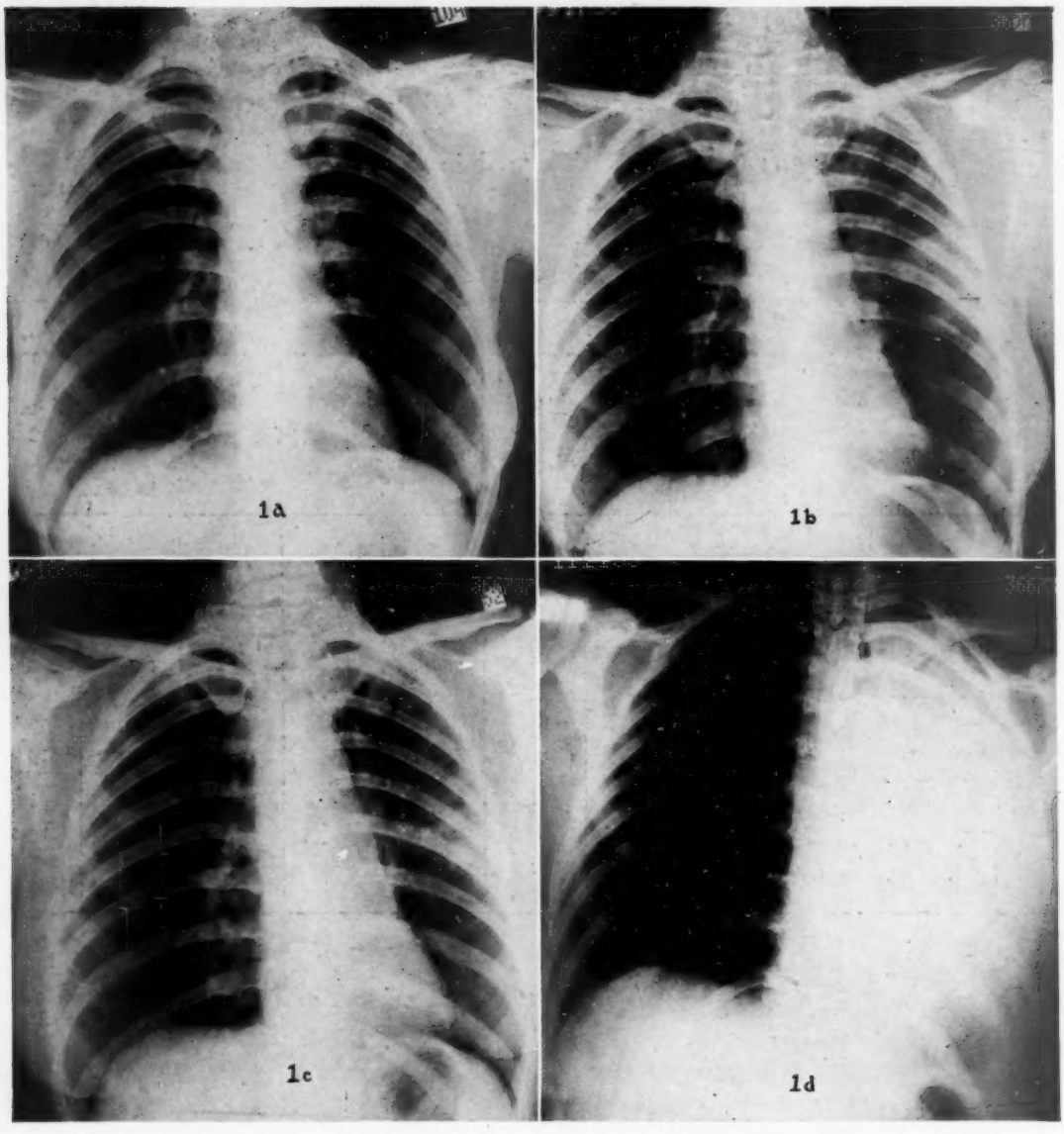

FIG. 1. Case I. *a*, August 14, 1935: minimal pulmonary tuberculosis, left apex. *b*, September 17, 1935: parenchymal infiltration, possible early atelectasis, left 3rd–5th ribs in the axilla, in addition to former lesion in the apex. *c*, October 18, 1935: mediastinal shift to the left, parenchymal lesion not markedly changed; suggestive of early bronchial obstruction. *d*, November 11, 1935: gross atelectasis of left lung.

(This patient is now dead; pneumothorax was induced with good response for a few months. Then followed periods of bronchial obstruction with high fever, relieved by evacuation of the retained secretions through the bronchoscope. Terminally the disease ruptured into the pleural space, resulting in an empyema, bronchopleural fistula and death.)

II. Spontaneous intermittent atelectasis.

CASE II. D. K., male, aged nine, No. 386044. A school survey reported a positive tuberculin skin test in the spring of 1935, and "chronic fibroid tuberculosis" in a chest roentgenogram of August 1, 1935. (This film was not available for comparison.) Admitted July 26, 1936, for treatment of tuberculosis of the left hip joint.

No signs or symptoms of pulmonary tuberculosis were noted in the history (save the

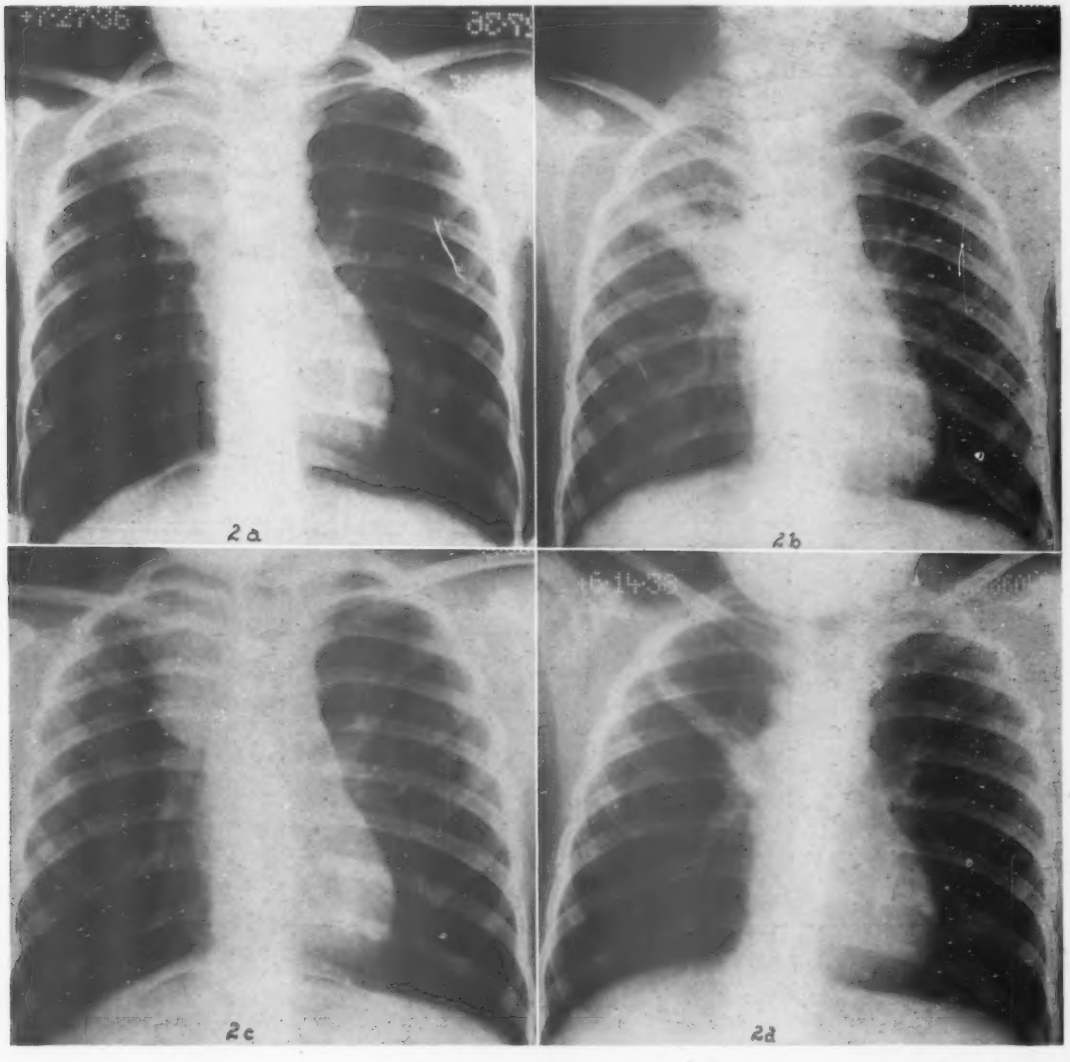

Fig. 2. Case II. *a*, July 27, 1936: atelectasis of superior lobe. *b*, January 18, 1937: partial re-aeration. *c*, March 30, 1937: recurrent atelectasis. *d*, June 14, 1938: re-aeration.

roentgenologic report and diagnosis). No record is to be found of stomach washings or sputum having been obtained or examined. (However the roentgenologic changes are almost classical for this type, hence the inclusion here.)

Roentgenograms of July 27, 1936; January 18, 1937; March 30, 1937; and June 14, 1938 (Figs. 2*a*, *b*, *c*, and *d*, respectively) demonstrate the fluctuating atelectasis of the right superior lobe. There was unquestioned evidence of loss of aeration, reduced volume with shift of the accessory fissure upward followed by partial re-aeration and improved volume. The atelectasis recurred followed by subsequent re-aeration. It is improbable that an hilar adenopathy could have induced such changes, particularly without evidence of such nodular mass upon the roentgenogram.

This case must therefore be considered as one of stenosis of the superior bronchus, probably of the hyperplastic type of tuberculous bronchitis.

III. Excessive reduction of volume and air content with collapse therapy, in reference to the extent of roentgenographic evidence of disease.

(*a*) *Following phrenicectomy:*

Case III. L. H., female, aged twenty-seven, No. 309768 (Barnwell, Littig and Culp's Case 4). Ease of fatigue and weakness for two to three years had been accompanied by attacks of wheezing, dyspnea and cough for the last

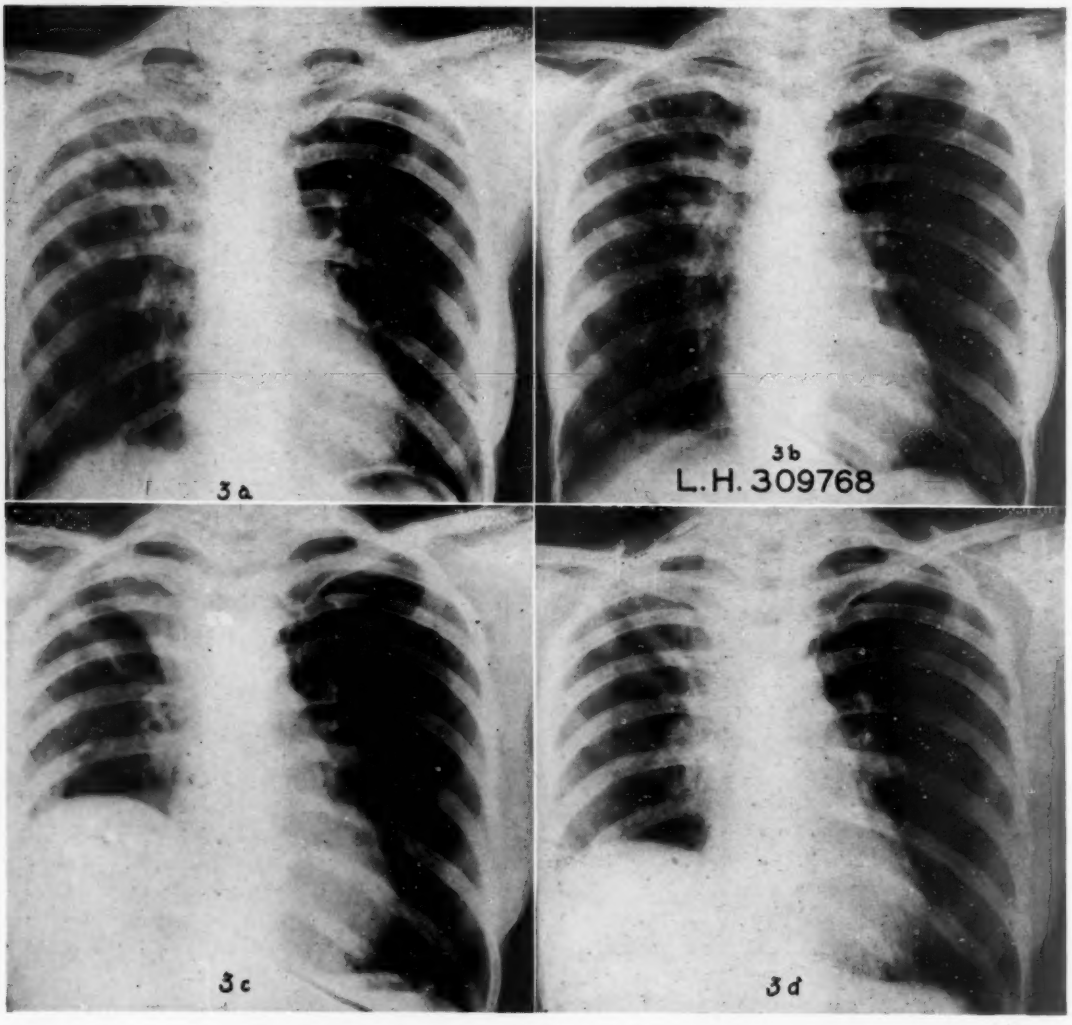

FIG. 3. Case III. *a*, March 10, 1933: moderately advanced right pulmonary tuberculosis; partial atelectasis of the superior lobe, right. *b*, March 29, 1933: some improvement in aeration. *c*, August 30, 1933: increased atelectasis following phrenicectomy. *d*, September 29, 1933: some improved aeration of superior lobe, but persistent atelectasis of median apical segment.

eighteen months. All symptoms increased during the two months prior to admission.

Upon examination there were rhonchi, râles and friction rub in the right thorax with dullness in the posterior apex; 5–10 gm. sputum daily, positive for acid-fast organisms, although they were not numerous.

Roentgenograms: March 10, 1933 (Fig. 3*a*): moderately advanced right pulmonary tuberculosis with elevation of the accessory fissure, partial atelectasis of the superior lobe. March 29, 1933 (Fig. 3*b*): some improvement in aeration.

Right temporary phrenicectomy, April 11, 1933, was followed by a sharp recurrence and increase in the atelectasis of the superior lobe. The symptoms did not improve, although the sputum for a time contained no acid-fast bacilli. (A rapid shift from positive to negative sputum in the presence of moderately extensive tuberculosis must suggest a block of the bronchus from the involved area.)

Roentgenogram of August 30, 1933 (Fig. 3*c*) demonstrates the atelectasis of the period following the phrenicectomy.

Bronchoscopy, September 6, 1933: extensive tuberculous tracheobronchitis with stenosis of the right bronchus, some stenosis of the left but

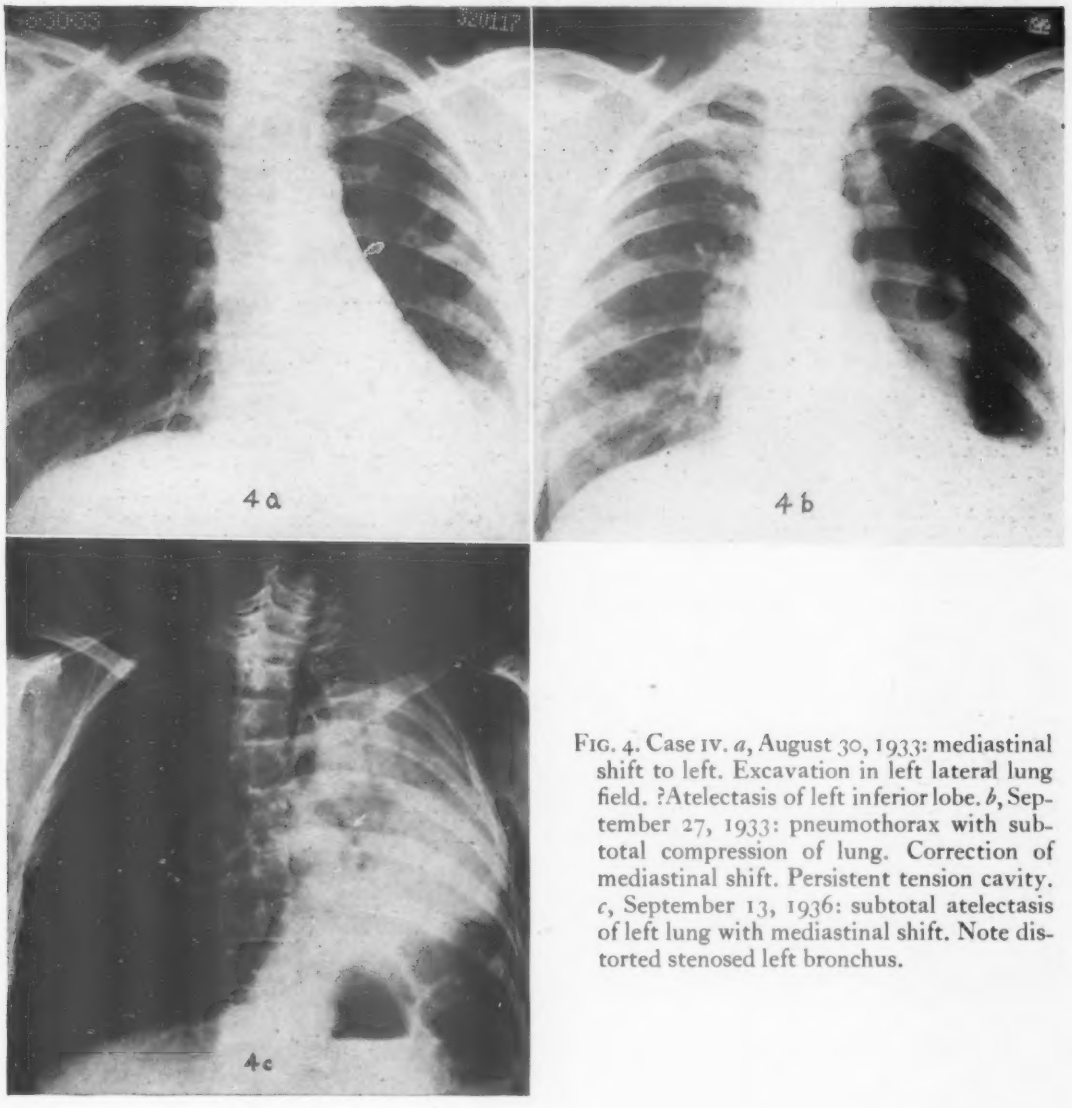

Fig. 4. Case iv. *a*, August 30, 1933: mediastinal shift to left. Excavation in left lateral lung field. ?Atelectasis of left inferior lobe. *b*, September 27, 1933: pneumothorax with subtotal compression of lung. Correction of mediastinal shift. Persistent tension cavity. *c*, September 13, 1936: subtotal atelectasis of left lung with mediastinal shift. Note distorted stenosed left bronchus.

admitting the bronchoscope. Several small ulcerative lesions along the thickened mucosa.

Roentgenogram of September 29, 1933 (Fig. 3*d*) revealed some improvement of the aeration in the superior lobe, but a persistent atelectasis of the median apical segment.

Symptoms were somewhat improved after the expectoration of a bronchial plug, about 7 mm. in diameter, early in October.

Comment. The clinical and roentgenologic signs correspond rather closely in this case. The patient obtained greater benefit as regards alleviation of symptoms after bronchoscopy than from the phrenicectomy.

In this case, also, there was bronchoscopic evidence of left bronchus involvement with no gross roentgenographic evidence of material change, a not uncommon feature of the disease. (The patient was last seen in the summer of 1938. She had no cyanosis, looked well. Right upper lobe was still reduced in volume, but improved in aeration. Right diaphragm high but functioning with limited excursion.)

(*b*) *Continued subtotal atelectasis of a whole lung following abandonment of a pneumothorax, tension or "tennis ball" cavity:*

Case iv. M. L., female, aged fifty-four, No.

320117. No record of physical findings at time of initial roentgenogram.

August 30, 1933 (Fig. 4*a*): heart and mediastinum shifted to left with some elevation of the left diaphragm, thin-walled, spherical cavity in the lateral lung field, plane of the second interspace and third rib, anteriorly. Atelectasis of left inferior lobe suggested on the films, not positively demonstrated at the time.

September 27, 1933 (Fig. 4*b*): pneumothorax had induced a subtotal atelectasis of the lung, some apical adhesions suspended it from the pleural dome. The mediastinal shift was corrected. Although there were no evident adhesions arising over the cavity to suspend it, and it had shifted in position with the lung in collapse, the cavity maintained its size and spherical or "tennis ball" contour. (This type of excavation, with insufficient peripheral infiltration to produce a rigid wall, we now believe to be suggestive of bronchial obstruction.)

Pneumothorax was lost when the patient returned home, refusing further hospitalization or sanitarium care, the upper lobe re-expanded but not the cavity.

In July, 1935, a left temporary phrenicectomy was accomplished, the sputum becoming negative for a time, but the patient subsequently complained of cough and wheezing. A rapid reduction in volume of the superior lobe as well as the lower was observed at that time, arousing suspicion of bronchial obstruction.

She returned in March, 1936, with complaints of cough and wheezing following a "cold" accompanied by sore throat, pleuritic pain and blood-streaked sputum the preceding month. The entire left chest was dull, with decreased breath and voice sounds and tactile fremitus. A few post-tussive râles were heard. The sputum was again positive.

Bronchoscopy, March 14, 1936, revealed an ulcerative and partially stenotic left tuberculous bronchitis.

She made an uneventful recovery from a cholecystectomy for cholecystitis with cholelithiasis in July, 1936. Sputum was positive at that time, but she refused any chest therapy. Vital capacity 1,300 cc., sedimentation index 0.9 mm. per minute.

The roentgenogram of September 13, 1936 (Fig. 4*c*) presents a gross shift of the mediastinum into the left hemithorax, elevation of the left diaphragm and subtotal atelectasis of the left lung. The distorted, stenosed left bronchus is visible by virtue of its air content in the compact airless lung.

Comment. In retrospect, the tuberculous bronchitis should have been suspected in 1933 because of the atelectasis. The later disappearance of the cavity was probably the result of the completion of its bronchial stenosis during the period of the pneumothorax.

(*c*) *Compression of lung about multiple thin-walled cavities by pneumothorax, persistence of sputum, subsequent demonstration of bronchial stenosis.*

CASE V. W. B., male, aged twenty-one, No. 345722. Ease of fatigue, chronic "cold" for one year, accompanied by a dry cough becoming productive three months before admission. Loss of 20 pounds in weight. Physical examination reported negative, except for grossly tenacious, purulent sputum containing 25–100 acid-fast bacilli per high-power field.

Admission roentgenogram, September 24, 1934 (Fig. 5*a*): multiple, thin-walled cavities with other minimal parenchymal and peritruncal infiltration in the left lung. Far-advanced pulmonary tuberculosis, left.

Pneumothorax, instituted early in October, compressed the lung about these cavities, which retained their size and spherical contour for some time (Fig. 5*b*, October 10, 1934).

Although the patient gained weight, and the lung was progressively compressed under sanitarium care, the sputum remained positive and of the same quantity, Subtotal atelectasis of the lung was demonstrated in the roentgenogram of April 17, 1935 (Fig. 5*c*).

Bronchoscopy on August 3, 1935, revealed marked, pliable, exuberant granulation tissue, bleeding readily, in the left bronchus, whose lumen was reduced to 5 mm. or less.

Concentrated sputum specimens remained positive, and in April, 1936, the amount of sputum had increased with increase in numbers of bacilli. Cough had increased.

Bronchogram on April 3, 1936 (Fig. 5*d*) demonstrated the marked stenosis of the left bronchus just distal to the carina tracheae, with more or less deformity of the lumen of the lesser bronchi. The lung remained compressed. Considerable effusion had developed in the pleural space.

Throughout the subsequent course of the patient's illness, his recurrent periods of in-

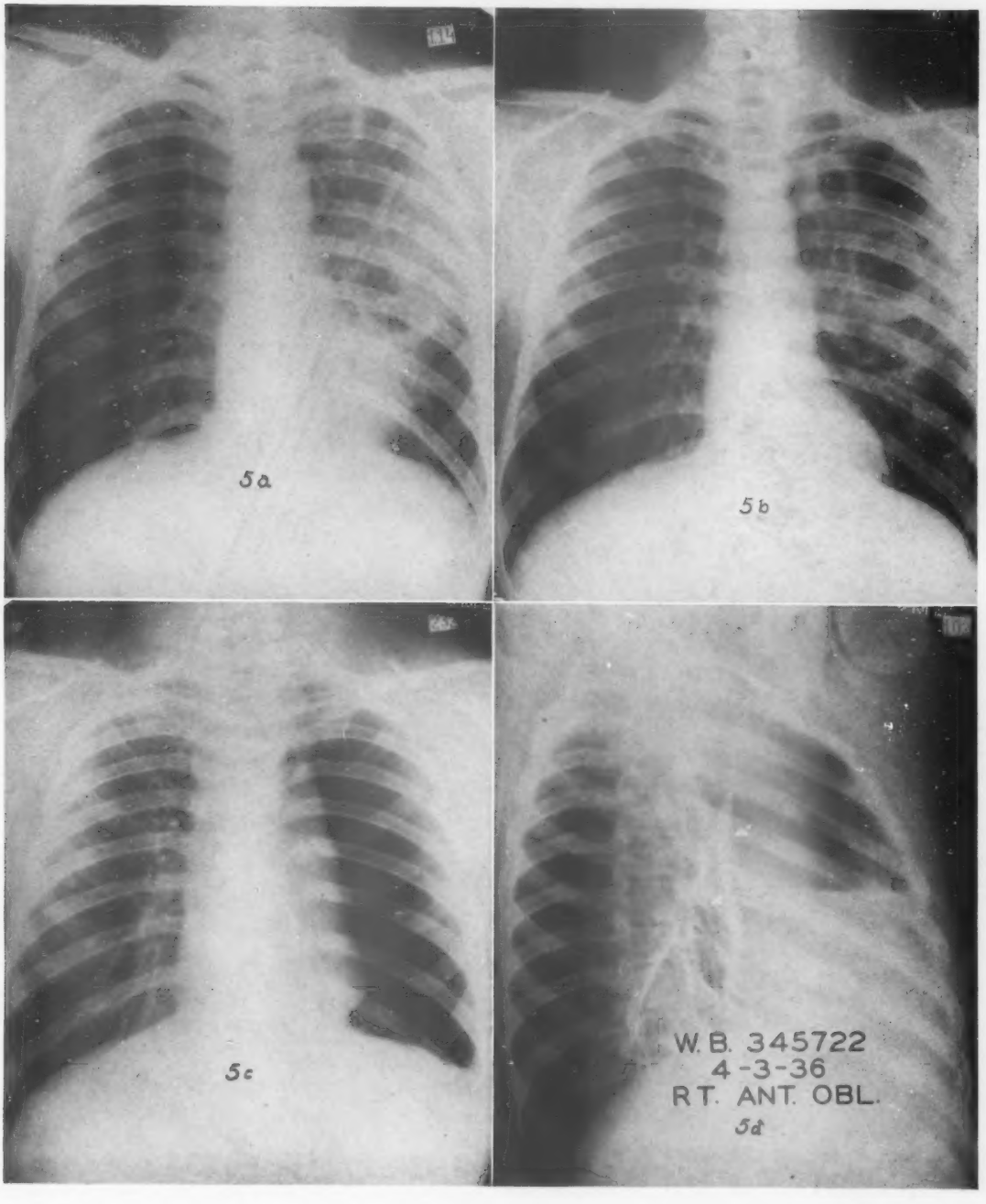

Fig. 5. Case v. *a*, September 24, 1934: far advanced left pulmonary tuberculosis with multiple apparent cavities. *b*, October 10, 1934: persistent multiple excavations with remaining lung compressed about them by pneumothorax. *c*, April 17, 1935: subtotal atelectasis; sputum still positive. *d*, April 3, 1936: bronchographic demonstration of stenosis of left bronchus.

creased malaise and elevation in temperature were relieved by bronchoscopic drainage of the stenotic left bronchus. Ulceration was observed on December 2, 1936.

Comment. The apparent minimal involvement of the lung in the early period (except for the excavations), the persistence of the spheroid contour of the latter after pneumothorax was instituted with greater initial compression of the relatively unin-

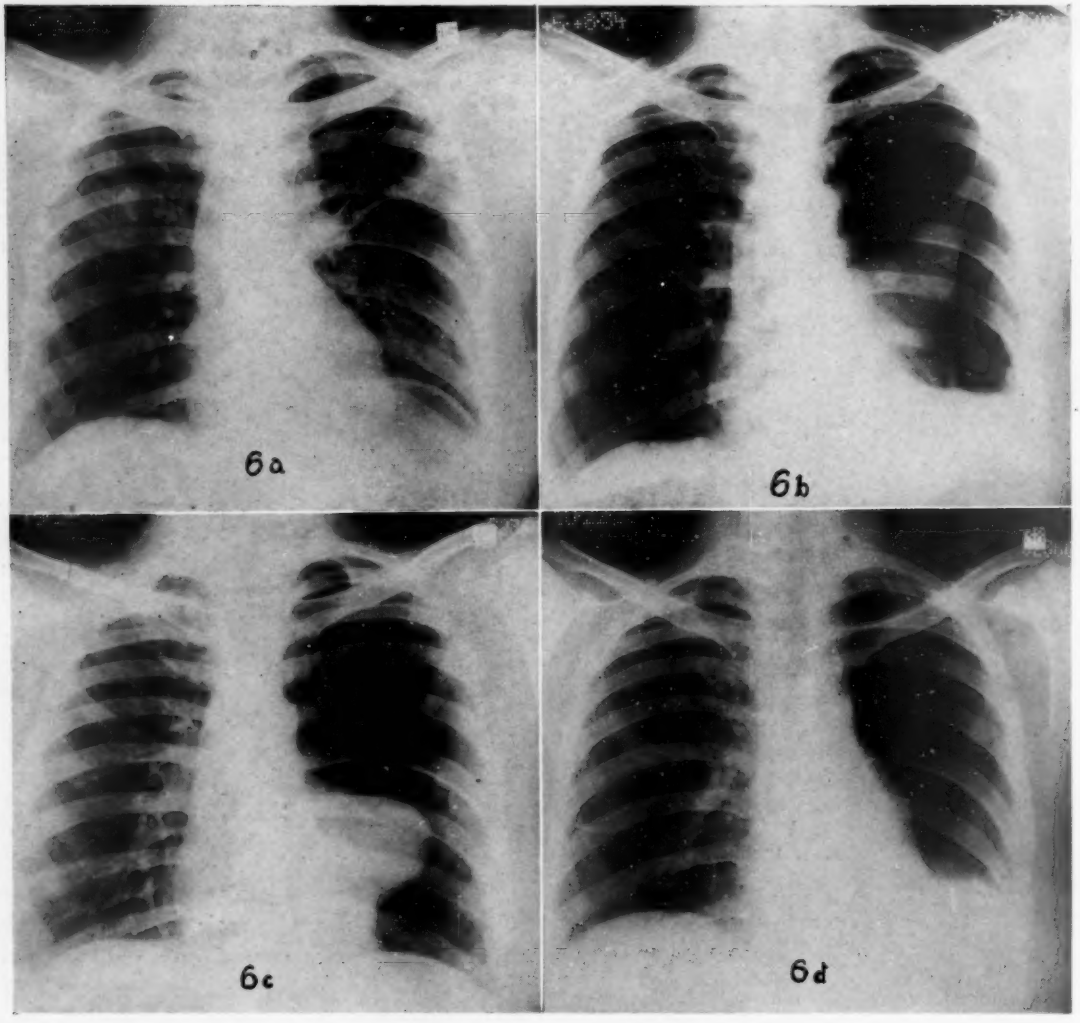

FIG. 6. Case VI. *a*, March 8, 1934: minimal parenchymal lesion, left mid-axillary lung. *b*, May 8, 1934: marked compression of left lung by pneumothorax; interpleural adhesions. *c*, August 8, 1934: re-expansion of inferior lobe following pneumonolysis, but increased dyspnea. *d*, October, 1935: subtotal atelectasis; wheezing persisted.

volved parenchyma than then excavated, the persistence of sputum in amount and character in spite of this collapse are strongly suggestive of bronchial involvement.

(*d*) *Minimal evident parenchymal lesion, relatively excessive de-aeration of lung and increase of symptoms with collapse therapy.*

CASE VI. L. G., female, aged thirty-three, No. 323608 (Barnwell, Littig and Culp's Case 5). Fatigue and cough for seven months following a "cold," with fever and night sweats. Increase in cough, with sputum, right pleural pain and loss of weight for the past four months.

On admission the patient had a tuberculous laryngitis. The sputum was positive. Expansion of the two sides of the thorax was equal, percussion note slightly impaired over the left apex, occasional râles were heard in the axilla, and the patient was aware of wheezing respiration.

Roentgenogram of March 8, 1934 (Fig. 6*a*) demonstrated a minimal parenchymal lesion in the left upper mid-axillary lung field.

Upon induction of pneumothorax (with some difficulty due to an angioma of the axilla—note calcareous deposits in the left thoracic wall), a marked compression of the entire left lung ensued (Fig. 6*b*, May 8, 1934). This was out of proportion to the previous apparent extent of the parenchymal involvement.

Following intrapleural pneumonolysis (Au-

gust 8, 1934) the inferior lobe re-expanded, but the patient's dyspnea increased.

The larynx had begun to improve in June. Wheezing respiration continued.

Bronchoscopy on January 12, 1935, revealed ulceration of the left bronchial mucosa with granulation tissue, exudate and multiple tuberculomata. Further bronchoscopy on February 7 suggested that the ulcerative lesions began about 2.5 cm. below the carina in the left bronchus.

Sputum varied from 12 to 40 gm. daily, positive on direct smear until August, 1935. A series of daily sputum examinations in November, 1935, was negative for tubercle bacilli on several days. Roentgen therapy had no appreciable effect.

In October, 1935, there was again a subtotal atelectasis of the left lung with some pleural effusion (Fig. 6*d*). (The patient is still alive with hydropneumothorax. Wheezing has persisted.)

Comment. The roentgenographic evidences of disease on the initial study were disproportionate to the sputum and symptoms. The massive compression of the early pneumothorax, the increase of dyspnea in the presence of re-expansion of the inferior lobe following the pneumonolysis, and the later re-collapse of the inferior lobe, with fluctuation of the sputum between positive and negative, subsequent to the section of the adhesions, and full collapse of the superior lobe in August present an epitome of the findings common to this complication of pulmonary tuberculosis.

DISCUSSION

The character of the excavations within the tuberculous lung is of importance. The presence of the tension or "tennis ball" type of cavity, to which we have alluded above, is suggestive of intracavitary tension by valvular obstruction of its bronchus, hence theoretically it should be more common in patients with tuberculous bronchitis.

The often relatively minor roentgen evidence of parenchymal disease in the presence of advanced tracheal and bronchial tuberculosis must also be emphasized. Here the sputum and the complaints of cough, wheeze and dyspnea, with more or less cyanosis are important, and may refute the opinion of a minimal lesion gained from roentgenograms. Also, as we have noted in the cited cases, sudden disappearance of sputum or marked fluctuation in amount of sputum should suggest bronchial block.

We have seen in this group varying degrees of airlessness of lung, from rapid progressive loss of pulmonary air content and volume, through fluctuating periodic airlessness to persistent subtotal collapse or complete atelectasis. These several stages have been accompanied by more or less mediastinal shift (dependent upon degree of de-aeration and previous fixation of the mediastinum) and elevation of the diaphragm on the side of greater involvement.

In uncomplicated collapse by means of intrapleural pneumothorax, the lung should retain its ordinary respiratory fluctuation in volume to some degree, at least until sufficient intrapleural pressure exists not only to reduce the tidal exchange of air but also to reduce or obliterate the residual air, and upon relaxation of the counter-pressure of the pneumothorax will re-expand so far as the disease process within the lung will permit. When, therefore, the collapse of a lung or one of its segments is disproportionate to the extent of the apparent pre-existent lesion, or re-expansion does not follow abandonment of such collapse measures (in the absence of evidence of extension of the disease and of a grossly rigid visceral pleura), obstruction of the tributary bronchial tree is to be assumed.

The existence of sufficient contractile tissue within the lung to accomplish relatively complete airlessness is doubtful, without at least balancing or exceeding the atmospheric pressure of air entering the trachea and bronchi plus the suction effect of the respiratory act upon the gaseous content of the lung. Therefore, relatively complete and rapid de-aeration and shrinkage of a lung or its segment upon phrenicectomy, pneumothorax or thoracoplasty cannot be looked upon as a normal reaction. The reduction in volume of a portion of lung which is appreciably greater than

the actual tissue apparently infiltrated by local disease and exudate (and therefore the site of at least local consolidation) by collapse measures, which do not exceed the sum of the atmospheric pressure plus the force applied by the respiratory action of the thoracic wall and diaphragm, must be an attempt to effect an intrapulmonary gas-pressure balance in the presence of bronchial obstruction to the inrush of air.

We would therefore consider a disproportionate selective collapse, or a spontaneous atelectasis as suggesting the probability of tuberculous bronchitis.

SUMMARY

Tuberculous tracheobronchitis exists with sufficient frequency to demand the attention of roentgenologists. Upon examination of serial chest films, the complication may be suggested or indicated to the roentgenologist by any one of the following:

1. Atelectasis.
2. Spontaneous intermittent atelectasis.
3. Extent of roentgen pathology not compatible with clinical course.
4. Degree of collapse greater than expected from evident lesion.
5. Sudden increased atelectasis with collapse therapy.
6. Visible changes in bronchi.
7. Oechsli's sign.
8. "Tennis ball" cavity.
9. Lobular emphysema in a patient with positive sputum.

Although it presents a fairly definite clinical entity, it can be diagnosed during life, with certainty, only by the bronchoscopist.

The assistance of Dr. John B. Barnwell, Associate Professor of Medicine, University of Michigan, in this study is gratefully acknowledged.

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DISCUSSION

DR. CHARLES R. AUSTRIAN, Baltimore, Md. It is a pleasure to be invited to discuss so clear a presentation of a timely topic as you have just listened to. However, at the same time it is difficult to discuss it because Dr. Peirce and Dr. Curtzwiler have been so complete in the context of their communication. Perhaps I can serve my purpose best by re-emphasizing some of the points and making a few additional ones.

I do not wish to be trite but I think that you will be impressed with the fact that a review of the symptoms emphasizes what has been said before, that all that wheezes is not asthma. It is time that the term asthma be limited more and more to the hypersensitive patient who has the symptom of dyspnea, paroxysmal in type, wheezing, rhonchi, and a paroxysmal cough. There is one point about the dyspnea that patients with tracheobronchial obstruction present which should be reiterated, and that is that quite frequently the patient is objectively extremely short of breath but subjectively seems to mind that shortness of breath very little.

A second point is that not infrequently the symptoms from which he suffers are augmented appreciably by a change in position.

A third point is the extreme variability of the symptoms from time to time regardless of surrounding conditions.

The real contribution, in the main, it seems to me, that the roentgenologist and the roentgenographic study of these individuals gives, is the demonstration of a hindrance to the ebb and flow of air, the normal ebb and flow through the airway. If, as has been indicated so well by the presentation of these patients, there is an appreciable obstruction to the flow of air through the lobar or major bronchi, varying degrees of deficiency of aeration of the lung will result.

This enables us by means of the film to determine that there is insufficient aeration of a segment or of the entire lung and to suspect that there must be something in the tube which leads the air to the parenchyma to hinder the ingress or the egress, or both, of air. If that hindrance is complete, one gets more or less complete so-called atelectasis (I will not be a purist this morning) of the segment supplied. If there is a complete hindrance of air through the lobar bronchus of a normal lung, one should get more or less complete collapse of the segment interfered with, but if, as Van Allen pointed out, the hindrance is to aeration through a bronchus smaller than a lobar bronchus under ordinary conditions, so-called collateral breathing prevents the development of such collapse.

However, in a disease such as pulmonary tuberculosis where even though the parenchymal change may be relatively slight, such collateral breathing may be interfered with and it is possible, therefore, under these conditions to get pulmonary collapse even though an obstruction occurs in a bronchus smaller than a lobar one. Whether or not that can lead to lobular atelectasis I think is a point that is still moot. The classical manifestations of atelectasis of the lung or of a lobe are so well known that reference to them is unnecessary.

In these instances fluoroscopy is often helpful to confirm one's judgment that it is atelectasis and not consolidation with which one deals, although he may feel that is true because of the diminished volume as evidenced by the film, because of the fact that during inspiration, the dislocation of the mediastinum toward the affected side will be increased, whereas during expiration, or forced expiration, the reverse will be true.

But not all patients who have bronchial or tracheobronchial obstruction have complete obstruction, and quite frequently, as has been indicated, there is obstruction that varies from time to time. One of the signs helpful in the diagnosis of such a state as this is the extreme and rapid variability of the manifestations of hindrance, as evidenced by the roentgenographic changes, by the symptoms and by the sudden disappearance of tubercle bacilli from the sputum, where there has been no concomitant improvement to lead one to suspect an anatomical cause for that change.

If there is valvular hindrance so that the ingress of air is relatively free as contrasted with the egress of air, then one may get the opposite of collapse, namely, hyperinflation or emphysema, loosely called. It is really hyperinflation of the segment aerated by that bronchus. Now and again, in patients with the symptoms and with the manifestations that have been described so well, one gets instead of collapse, hyperinflation and must be prepared to utilize that finding as a corroborative bit of evidence.

The type of cavity to which reference has been made is, I think, considered by all those who have been studying the condition a most useful one, and I wish to add only one statement to that made by Dr. Peirce, that the presence of a spherical or spheroid cavity with thin walls, with or without a fluid level that fails to collapse when collapse therapy is induced, is diagnostically of maximum importance, provided there are no demonstrable adhesions that may have prevented the collapse of the cavity that would otherwise have gone down without obstruction to the bronchus.

The value of knowing the paradoxical effects, if you please, of induced pneumothorax and similar types of collapse therapy on lungs that are tuberculous when there is obstruction has been brought out quite clearly and is of great importance. If all patients who had tracheobronchial tuberculosis had either complete, varying, or valvular obstruction, our problem would be a little simpler but unfortunately, there is a group in which this type of disease, this localization of tuberculosis causes no appreciable hindrance of the inflow or outflow of air and therefore offers a real difficulty.

Hopkins, at the meeting of the National Tuberculosis Association in Los Angeles in June, pointed out in a series of some five hundred-odd patients with pulmonary tuberculosis, that bronchoscopic examination has shown the presence of bronchial lesions in a little over 30 per cent. Of these, 6 per cent showed roughly no evidence of obstruction at all and therefore in this group, one would be deprived, by roentgenography at least, of the evidence either of collapse or of hyperinflation, and would have to take recourse primarily to one other valuable contribution of the film, namely, as has been pointed out, the great discrepancy between the symptoms, the physical signs and what was depicted on the film of the chest.

Finally, there is another variety, the type in which only the very small bronchi seem to be involved, the so-called bronchiolar type, or in the smaller branches before the bronchioles

are given off, in which one may have extreme dyspnea, moderate cyanosis, large quantities of sputum rich in tubercle bacilli, without any demonstrable diagnostic evidence on the film which presents an appearance not unlike that seen in many cases of bronchiectasis.

I cannot help feeling that what the roentgen ray shows oftentimes in patients with this syndrome is very like what a certain type of artist attempted to depict by his technique in the advertisements with which we were so familiar in the last decade, where, with a minimum of line, to the receptive mind a maximum of suggestion was given. It is the negativity rather than the positiveness of the film that in given cases usually furnishes most of the evidence.

No reference has been made to bronchography and I think perhaps happily, although it has been utilized in a number of these patients by different observers, not without a certain amount of hazard, I feel. However, it has been employed and in a number of instances it has been reported that the definite presence of obstruction, and its localization has been made manifest in this way. Personally, I have had no experience with it in these patients and would hesitate, I think, to employ it.

Finally, I would say, in epitome, that symptoms lead to a suspicion of the existence of tracheobronchial tuberculosis and the roentgen ray makes the presumption extremely strong provided, of course, one has excluded or can exclude other causes of bronchial obstruction. Thirdly, it is by means of the examination of the sputum and with the bronchoscope that the presumption may be proved to be true and the localization of the lesion determined.

DR. T. A. GROOVER, Washington, D. C. I would like very briefly to report one case that throws a rather interesting sidelight on this question of tracheobronchitis. About three years ago, a child about six years old was brought to us who for some weeks previously had had wheezing respiration. We made a roentgen examination of this child and found an obstructive emphysema on the right side. There was nothing else significant in the examination other than this obstructive emphysema. We naturally, and I think quite properly, made a diagnosis of non-opaque foreign body and the patient was referred to Dr. Jackson in Philadelphia for its removal. A few days later we got a report from Dr. Jackson that he had removed a grain of puffed wheat from the right bronchus and congratulated ourselves on the diagnosis which we had made. A short time after that, we got a communication stating that on further examination of this material, removed from the bronchus, they found it to be a tuberculous mass of tissue and this was later confirmed by animal inoculation.

Subsequent to that, the child did develop pulmonary infiltration, in the region of the right hilum which roentgenologically had the appearance of tuberculosis. This ultimately cleared up and the child now is apparently well.

DR. JOHN SPROULL, Haverhill, Mass. Prior to 1928, there were no reports in the English literature regarding collapse of the lung in adult pulmonary tuberculosis. In 1928, in the AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY, I reported 4 cases of collapse of the lung as a complication of adult pulmonary tuberculosis, and one of these cases was bronchoscoped. At that time, bronchoscopy was not often carried out in tuberculosis and I had some difficulty in getting a bronchoscopist to bronchoscope the patient.

Prior to that time, in such cases the shift of the heart to the affected side had been regarded as the result of fibrosis or previous pleurisy. I had a patient at that time who showed a sputum positive for tuberculosis and who also showed collapse of the lower lobe of the right lung. I was able to observe her every two or three days until she also developed collapse of the upper lobe of the same lung. I was rather interested to know the cause of the collapse and so had bronchoscopy performed.

The bronchoscopy recorded by Dr. Richards of the Peter Bent Brigham Hospital in Boston showed inflammatory edema of the bronchus, and there was some question at that time as to whether the bronchostenosis was the result of external pressure from enlarged glands or whether it was the result of inflammation of the mucous membrane of the right main bronchus.

I communicated with the late Dr. Manges of Philadelphia at that time and he said he had never seen collapse of the lung as a complication of adult pulmonary tuberculosis. He had seen it in childhood due to glandular pressure. It is only fair to state that I did not recognize the pathologic condition as tuberculous bronchitis, but the films were similar to those of the cases here presented by Dr. Peirce which showed complete collapse of one lung.

Since that time, in attending seminars at the

Massachusetts General Hospital and in private practice, I have seen many cases of collapse of the lung in pulmonary tuberculosis, and bronchoscopic examination has revealed in many cases obstruction of a bronchus from granulation tissue. I do not know of any cases wherein opaque bodies such as Dr. Hopkins spoke about have been demonstrated in the bronchi. It is well known that inflammatory edema and granulation tissue in a bronchus occurring as the result of tuberculosis can produce a roentgen picture similar to an obstructing foreign body in the bronchus.

Dr. George E. Pfahler, Philadelphia. I would like to ask whether in any of these cases roentgen treatment has been utilized. It does seem that with the granulation tissue which has just been described, located in these bronchi, as the cause of the obstruction, a moderate amount of irradiation might be helpful.

Dr. Sproull: I might say something on that. I suggested that it might be if these were due to glandular enlargement, but in the cases that I saw and in which I tried it, it did no good.

Dr. Peirce (closing). I wish to thank Dr. Austrian very much for the generous discussion of our paper, and his kind comments.

I apologize to Dr. Sproull for not having found his previous report. It commonly has been my good fortune, each time I say something here, to discover that it was said much better by someone else a long time before.

In regard to Dr. Pfahler's question, roentgen therapy has been tried. If Dr. Jacox is here, I wish he would discuss it. We thought that perhaps it might be of some benefit but I think I can say very definitely and frankly that it is not, and in some cases it has seemed to make the patients worse. I do not believe that irradiation has much to offer these patients. It may possibly in the hyperplastic cases; the type in which, as Dr. Sproull mentioned, there is edema in the early phase before formation of gross tubercles and before ulceration. But I am extremely disappointed in the results that we have obtained so far with irradiation. In fact, we are so disappointed in it that we feel at the present time the results warrant simply some mention with the statement that it has not had important beneficial effect.

I appreciate Dr. Groover's comment and the description of his very interesting case. The formation of tuberculoma in these individuals seems to be quite common, and I anticipate that is what that was.

Dr. Groover: Yes.

Dr. Peirce: I am glad that Dr. Austrian brought out the matter of obstructive emphysema. Dr. Barnwell and I have had considerable correspondence and discussion about it this summer, for it had been called to our attention. Recently, Dr. Barnwell wrote me that he had received, from some of the men who had been kind enough to send in cases for us to see, some films which showed this obstructive emphysema. We had not seen it in our series, or if we had, we passed it over; we have not been aware of it. I think it is another of these important suggestive signs. Dr. Austrian has emphasized the roentgen evidence. The clinical evidence oftentimes develops the suspicion and the roentgen evidence permits the presumption on the basis of discrepancy between the roentgen signs and the clinical signs or symptoms.

We have found that we were not examining our patients early enough after the induction of pneumothorax. Every such patient has a fluoroscopic examination, but we were not recording the situation on films. Another part of the problem that Dr. Barnwell is now working on is the comparison of inspiratory and expiratory films at the same sitting. These may give additional information. We hope to have some further report, and I anticipate that will come from Dr. Barnwell shortly.

ROENTGEN ASPECTS OF THE UPPER RETRO-ESOPHAGEAL PULMONARY BORDERS*

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IN THE upper portion of the thorax posterior to the esophagus the right and left pleural spaces closely approach one another under normal conditions. An appreciation of this anatomical fact is of importance in the interpretation of roentgenograms because the pulmonary borders in this region are sometimes outlined roentgenographically. Various physiological and pathological conditions may displace the medial pleural margins and cause difficulty in the identification of roentgen shadows. It is a rather common misconception that the pleural cavities are separated by a broad mediastinal septum posteriorly in contrast to the almost midline reflections of the mediastinal pleura anteriorly. This erroneous impression is strengthened by published cross-sectional diagrams of the thorax in anatomical treatises which often fail to show the true extent to which the pleural cavities protrude medially in some regions of the posterior part of the mediastinum. In the cadaver normal relationships may be distorted somewhat during the process of embalming unless special precautions are observed. Ordinary roentgenograms of the chest representing posteroanterior projections as a rule afford little opportunity to observe the mediastinal pleural relationships.

Heiss[4] studied the posterior pleural borders in the cadaver after the injection into the pleural cavity of a colored fluid mixture which would solidify. He then removed the vertebrae and adjacent portions of the ribs from a posterior approach and thus exposed the posterior part of the mediastinum. He demonstrated that above the level of the aortic arch and the arch of the vena azygos the pleural borders of the two hemithoraces are close together in front of the vertebral bodies and posterior to the esophagus. The mediastinal pleura of the right side especially lies very close to the median line at this site. The arch of the vena azygos interrupts the medial extension of the right pleural reflection at the level of the fifth thoracic vertebra. Again caudal to the arch of the vena azygos and extending to the level of the tenth thoracic vertebra there is a considerable extension of the right pleural cavity towards the left side in front of the vena azygos and thoracic duct and posterior to the esophagus. These right mediastinal pleural reflections overlap most of the thoracic esophagus when viewed from behind.

Danelius[2] applied a radiopaque substance to the parietal pleura in cadavers and compared the pleural lines so demonstrated with the shadows seen on the normal posteroanterior roentgenogram. He showed that as one traces the pleural borders of the pulmonary apex medially and downward, it extends on each side far into the vertebral shadow until at the approximate level of the fourth thoracic vertebra the pleurae of the two hemithoraces are almost in contact. This site of close proximity of the right and left mediastinal pleurae was in the upper posterior portion of the mediastinum in front of the vertebrae and posterior to the esophagus. Danelius also pointed out that because of this anatomical fact a portion of lung is projected upon the mediastinal density and is not to be seen in posteroanterior roentgenograms.

In a later paper Danelius[3] reported some clinical roentgenographic studies. By outlining the esophagus with barium, and by

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the use of lateral roentgenograms he came to the following conclusions: (1) A retro-esophageal space, that is, a space between the vertebral bodies and the esophagus which contains lung, can be demonstrated in the upper mediastinal region in most subjects. The space may be absent if the curve of the thoracic spine is slight. (2) The retro-esophageal space is larger during inspiration and smaller during expiration. The esophagus follows the trachea closely and moves forward during inspiration, thus increasing the distance between esophagus and vertebrae. (3) The retro-esophageal space is slightly smaller with the patient supine than in the erect position. Even with the patient recumbent, however, in most instances the esophagus does not rest directly on the vertebral column in this region.

The medial pulmonary borders in the upper posterior portion of the thorax cannot usually be visualized roentgenographically in routine posteroanterior projections because the aerated tissues are insufficient in amount to produce visible contrast. In denser roentgenograms produced with the aid of the Potter-Bucky diaphragm these pulmonary borders can sometimes be observed.

Fig. 1. Arrows indicate pulmonary borders in retro-esophageal space superimposed on tracheal outline. Mediastinal pleural borders posteriorly can be seen as continuation of pulmonary apex. At fourth thoracic vertebra pleurae of two sides are almost in contact behind the esophagus.

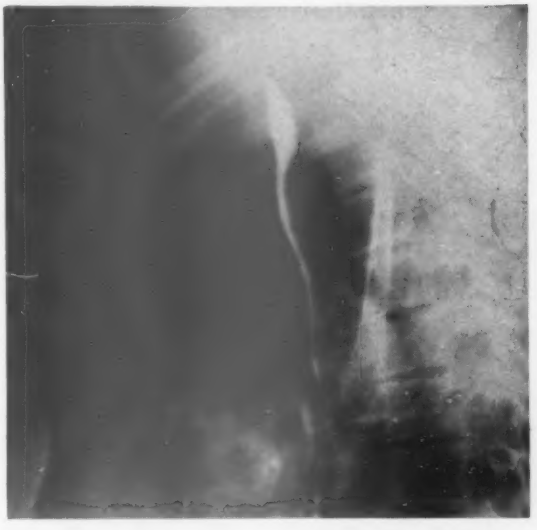

Fig. 2. Lateral roentgenogram with esophagus outlined with barium. Note retro-esophageal space contains pulmonary tissue above aortic arch.

If the mediastinal septum has not been displaced as the result of disease, the pleural borders in the posterior portion of the upper mediastinum are seen, if at all, as curved margins of aerated lung approximating each other close to the midline of the spine.[1] In instances in which the retro-esophageal protrusion of the lung can be visualized roentgenographically it will be seen to be a continuation of the medial pulmonary borders as the outline of the apical portion of the lung is traced medially and downwards into the mediastinal densities. These margins are usually superimposed on the area of diminished density which represents the air column within the trachea (Fig. 1). Between the level of the third and fifth thoracic vertebrae the pleural borders normally overlap the vertebral column. The point of closest approximation between right and left lungs posteriorly occurs at the level of the fourth thoracic vertebra. The medial extension of the lungs posteriorly is limited below by the arch of the vena azygos on the right and the aortic arch on the left. Pulmonary

Fig. 3. Arrows indicate margins of retro-esophageal portion of lungs in case of right apical pulmonary tuberculosis associated with emphysema.

tissue in the retro-esophageal space is seen to best advantage roentgenographically in lateral projection (Fig. 2).

The distance between the upper esophagus and the anterior vertebral surface is increased in subjects with thoracic kyphosis, and consequently the retro-esophageal space contains an abnormally large volume of pulmonary tissue. This fact can best be shown roentgenographically in lateral projections when the esophagus is outlined with ingested opaque material. If thoracic kyphosis is associated with emphysema of the pulmonary apices, conditions are most favorable for roentgenographic demonstration of the medial pleural borders in the upper posterior thorax. Occasionally under such circumstances the adjacent margins of lung may be identified in the routine frontal projections without the aid of the Potter-Bucky diaphragm (Fig. 3).

Since the mediastinal pleurae of the two hemithoraces are separated from one another by nothing more than a thin wall of areolar tissue in the retro-esophageal space, it is not surprising that this septum should be rather easily displaced to one side as the result of various pathological conditions within the chest. In a previous communication[5] it has been pointed out that mediastinal herniation may occur at this site when intrapleural pressures on the right and left side are unequal. Scar tissue contracture occurring in one pulmonary apex only, or more predominantly in one apex than the other, may cause traction on the mediastinal pleural septum resulting in its displacement across the midline. Under these conditions pulmonary displacement is associated with tracheal and esophageal shift in the same direction. This set of circumstances may produce mediastinal herniation. However, inequality in the intrapleural pressures of the opposing hemithoraces is undoubtedly a much more common cause. Upper posterior mediastinal herniation is encountered occasionally in patients with pulmonary tuberculosis (Fig. 4). In such an instance the herniated portion of lung may be incorrectly interpreted as representing a pulmonary cavity or emphysematous bulla of the other lung.

After the surgical removal of one lung numerous intrathoracic anatomical readjustments occur. Among those following left pneumonectomy, Rienhoff[6] describes the invagination of the posterior mediastinum by a lappet of the right lung in front of the bodies of the vertebrae but behind the esophagus. A part of the protrusion is above the arch of the azygos vein in the

Fig. 4. Arrows indicate border of right lung which has herniated through retro-esophageal space secondary to fibrotic tuberculous process in left apex.

region under discussion in this paper. The roentgenological appearance of the protruding portion of lung in the upper posterior portion of the mediastinum after pneumonectomy is seen in Figure 5. This roentgenogram was obtained several months after complete removal of the left lung because of a bronchial tumor associated with cystic destruction of the entire lung.

Although several instances of mediastinal herniation through the weak place in the upper posterior portion of the mediastinum have been observed in our clinic, these have all been in the same direction from right to left. We have never encountered an instance of herniation at this site in which the lung protruded into the right hemithorax. It may be that the aortic arch acts as a partial barrier against bulging toward the right since just below this region the aorta itself protrudes slightly towards the left and may limit the shift of the lung and mediastinum toward the right. Under normal circumstances the posterior mediastinal pleura on the right lies closer to the midline than does the pleura on the left.

Sometimes when seen in roentgenograms the posterior pulmonary borders are thought to represent the medial margins of lung anteriorly. In several published articles this erroneous assumption appears to have been made. Since the only point of close approximation between right and left lungs above the upper margin of the manubrium occurs posteriorly, it is obvious that when medial pulmonary margins can be made out close to the midline above the manubrium they must represent relationships in the posterior mediastinum. Except under most unusual circumstances the pleural borders do not approach the midline anteriorly above the superior margin of the manubrium. A clear understanding of these relationships is of advantage in differentiating anterior and posterior pulmonary borders as seen roentgenographically. Lateral shifting of visible pulmonary margins in relation to trachea or esophagus

Fig. 5. Roentgenogram obtained several months after left total pneumonectomy. Arrows indicate border of right lung which has protruded posterior to trachea and esophagus into left hemithorax. The outline of the anterior mediastinal hernia can be seen below the sternoclavicular level.

with various degrees of rotation about the vertical axis of the thorax serves to verify the relatively anterior or posterior position of visible pulmonary margins near the midline.

There is usually no difficulty in differentiating these pleural borders from the tracheal outline. The band of diminished density which represents the air column within the trachea can be traced upward into the cervical region and usually stands out rather clearly against the background of surrounding structures of greater density. The trachea is rarely as sharply curved at any point in its course as the pulmonary margins in this region may be. Furthermore, the pleural margins can usually be traced as a medial continuation of the pulmonary borders in the thoracic apex.

It is apparent when one studies the relationships of the pleura in the upper posterior portion of the mediastinum that an appreciable amount of pulmonary tissue in this margin may be hidden from view in the roentgenograms prepared in the usual

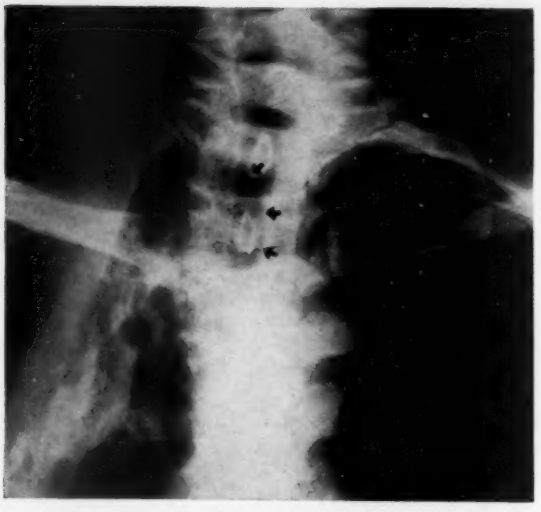

FIG. 6. Right upper thoracoplasty without apicolysis performed for pulmonary tuberculosis. Arrows indicate border of retro-esophageal portion of right lung.

posteroanterior projection. Obvious lesions localized to these medial portions of lung may easily escape notice even on otherwise adequate roentgen examination. No information is available as to the frequency with which lesions restricted to lung in this position occur. Cases of pulmonary tuberculosis have been observed, however, in which following thoracoplasty without apicolysis an appreciable amount of uncollapsed lung was present in the upper retro-esophageal space (Fig. 6). In a few such instances this was an important factor in inadequate surgical collapse of the tuberculous portion of the lung.

SUMMARY

1. The mediastinal pleurae of the two hemithoraces are in close proximity in a part of the upper posterior portion of the mediastinum between the esophagus and vertebrae.

2. The displacement of these pleural borders by various physiological and pathological processes is described.

3. The roentgenological interpretation of these pulmonary borders is discussed.

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AN ANATOMICAL, PATHOLOGICAL AND ROENTGENOLOGICAL STUDY OF THE INTERVERTEBRAL JOINTS OF THE LUMBAR SPINE AND OF THE SACROILIAC JOINTS*

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and

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I. ROENTGENOGRAPHY OF THE LUMBAR SPINE. AN EVALUATION OF THE OBLIQUE VIEW

THE value of the oblique projection of the lumbar spine, known as the "Dittmar position"[9] in European literature, was indicated by Meyer-Burgdorff[25] in his monograph on spondylolisthesis and by Hubeny[19] in this country in 1931. Since then, Ghormley and Kirklin,[13] Ghormley,[12] Hadley,[15] Morton,[27] Oppenheimer[32] and others have stressed its importance in the study of changes in the facets and apophyseal (intervertebral) joint spaces of the lumbar spine, the position and structure of the neighboring bone and neural arch, and the relation of the articular processes to the vertebral bodies and intervertebral spaces. Ghormley and Kirklin, and Morton have noted that it is possible to get a new view directly through the upper part of the sacroiliac joint, and suggested that this position might prove of value in the diagnosis of certain sacroiliac diseases. All authors advocate a 45° oblique position, although Ghormley and Kirklin recommended a position with the transverse axis of the pelvis at a 32° angle with the horizontal plane.

Arthritic changes involving the zygapophyseal joints become manifest on the roentgenogram by a loss of the smooth margin of the joint surfaces, diminution in the width of the joint space, and roughening and pointing of the articular processes. These changes, advocated by some (Putti,[33] Ghormley,[12] Oppenheimer[29,30,31]) as a cause of low backache and of the sciatic syndrome, have been noted during routine gastrointestinal and urinary tract roentgenographic studies in the absence of any history of local or radiating pain in the back.

Hadley[16,17] has discussed the diagnosis by means of the anteroposterior and 45° oblique views of the lumbar spine, of subluxations of the zygapophyseal joints with bony impingement of the upper end of the superior facet against the pedicle above, or of the lower end of the inferior articular process against the lamina below, and believes that such contact may cause pain in the back. Such subluxations he believes are either secondary to narrowing of the intervertebral disc or to increased lumbar lordosis. Morton has observed that the distance between the tips of the articular processes and adjacent bony structures normally diminishes progressively from above downward in the lumbar spine and lumbosacral area. That such subluxations of the articular facets with narrowing of the intervertebral foramina are more apt to follow exaggeration of the lumbar lordosis or narrowing only of the posterior part of the intervertebral disc as suggested by Ayres,[1] Williams,[45] and Williams and Yglesias,[46] is indicated by the following observation: If the entire intervertebral disc between two vertebrae is excised and the adjacent vertebral bodies approximated, the result is a separation of the facets and an enlargement of the intervertebral foramina, but if only the posterior portion of the disc is removed or if the lumbar segments are hyperextended, subluxation of the facets with

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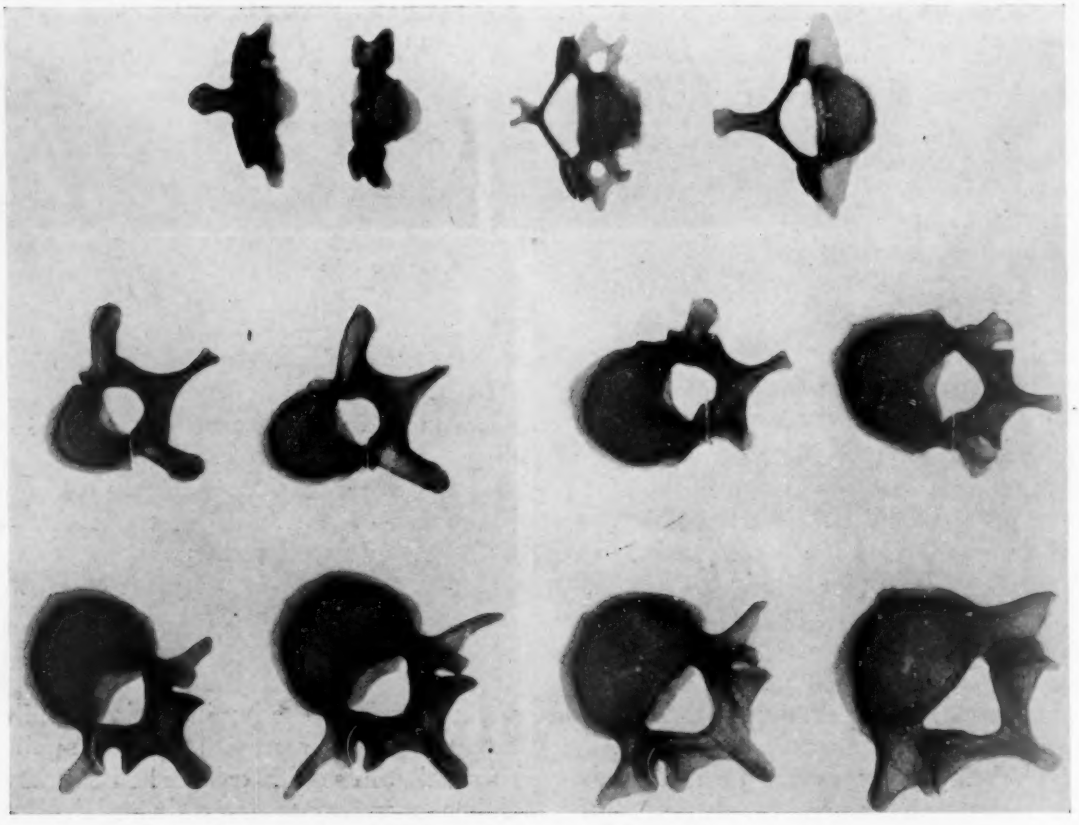

FIG. 1. Upper row (left to right)—2nd, 3rd, 5th and 7th cervical vertebrae. Middle row (left to right)—2nd, 5th, 8th and 12th thoracic vertebrae. Lower row (left to right)—2nd, 3rd, 4th and 5th lumbar vertebrae. The position of each vertebra indicates the position of the patient (the lower border of the figure representing the plane of the roentgen table) for best visualizing the facets and apophyseal joint spaces nearest the roentgen film. The plane of the superior facets of the cervical and thoracic vertebrae is flat; in the lumbar vertebrae it is concave.

constriction of the intervertebral foramina is seen to occur.

In our study, 25 human adult lumbar spines and pelves, all male, were denuded of their overlying soft tissues and were roentgenographed in the anteroposterior, lateral, and right and left 45° oblique planes, and where the transverse process of the fifth lumbar vertebra appeared to impinge on the ala of the sacrum or the ilium, a 45° oblique view of the lumbosacral region was taken from below upwards. These anatomic specimens were studied grossly with reference to changes in the bodies, accessory processes, apophyseal and sacroiliac joints and then sectioned in the midsagittal plane for study of the vertebral bodies, intervertebral discs, the spinal canal and its contents.

Extensive Paget's disease of the bone (osteitis deformans), involving the lumbar spine and pelvis, was noted in the roentgenograms of 2 specimens. The following conclusions were drawn following these comparative anatomical and roentgenological studies:

1. Facets and apophyseal (intervertebral) joints of the lumbar spine whose axes are other than 45° from the sagittal plane may falsely appear the site of pathological processes on the routine 45° oblique views. In 13 of the 25 specimens, although the apophyseal joints were grossly uninvolved, the 45° oblique roentgenogram strongly suggested pathological changes; in all of these specimens the angle of the joint line, measured from the sagittal plane, exceeded or was less than 45 degrees.

2. Accessory ossicles (epiphyses) at the tips of the articular facets are frequently not visualized on the roentgenogram, and one may infer that fractures in this region might also remain undiagnosed.

3. Degenerative changes in the intervertebral discs are noted on the roentgenogram only after they are advanced and associated with narrowing of the intervertebral space and marginal bony proliferation.

Nuclear herniations into the vertebral body are visualized only when they are surrounded by a zone of osseous sclerosis. Herniations of the intervertebral disc into the vertebral body (Schmorl's cartilage nodes), measuring from 4 to 8 mm. in diameter, were present grossly and evident roentgenographically in 3 instances; they were not visualized on the roentgenogram, although present in the gross specimen in 3 other instances.

4. Subluxations of the articular facets, as described by Hadley, occur most frequently with narrowing of the posterior part of the intervertebral disc. Apparent subluxations in the presence of intervertebral discs of normal height are due to bony proliferation of the articular margins of the facets.

5. The diagnosis of degenerative changes, especially of ankylosis, of the sacroiliac joint, by the roentgenogram, is frequently not corroborated by actual dissections. The 45° oblique projection penetrated directly through the upper part of the joint space in only 6 of 28 normal sacroiliac joints.

6. The oblique view of the lumbar spine is valuable in visualizing marginal prolif-

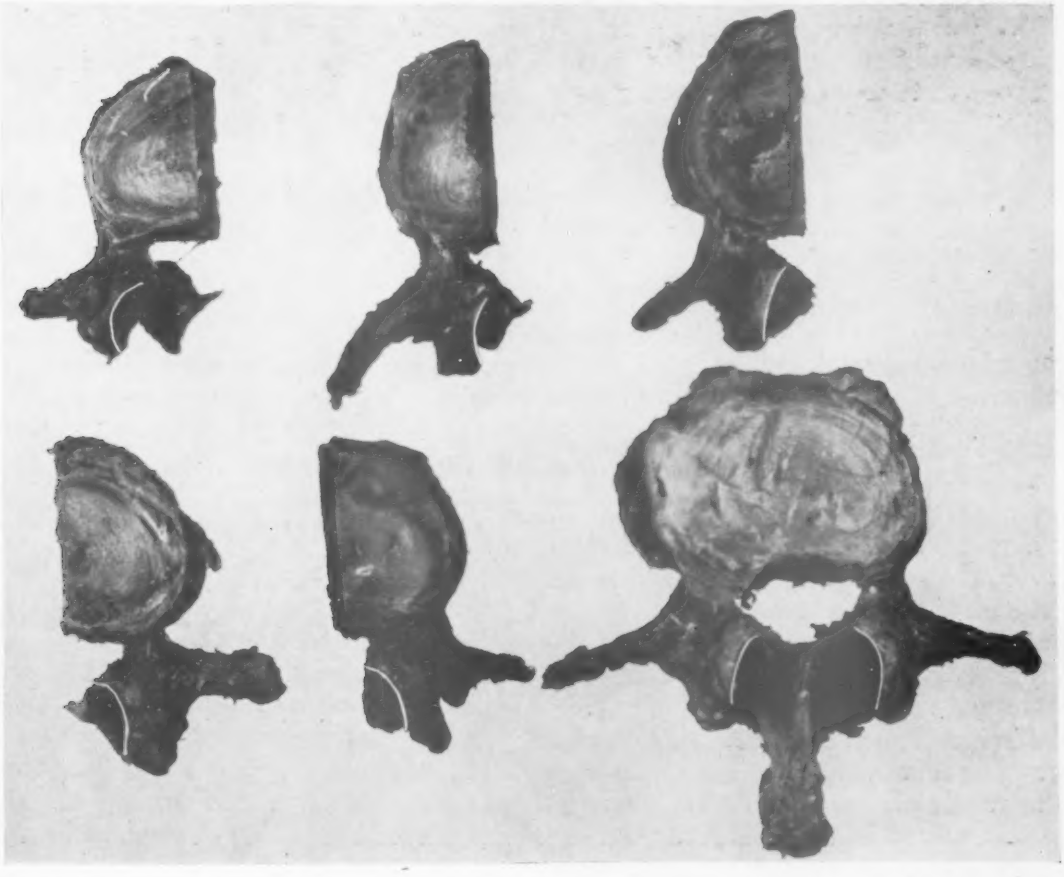

Fig. 2. Superior facets of the third lumbar vertebra. There is variation in the shape of the articular surfaces and in the angle of these surfaces from the sagittal plane of the vertebrae.

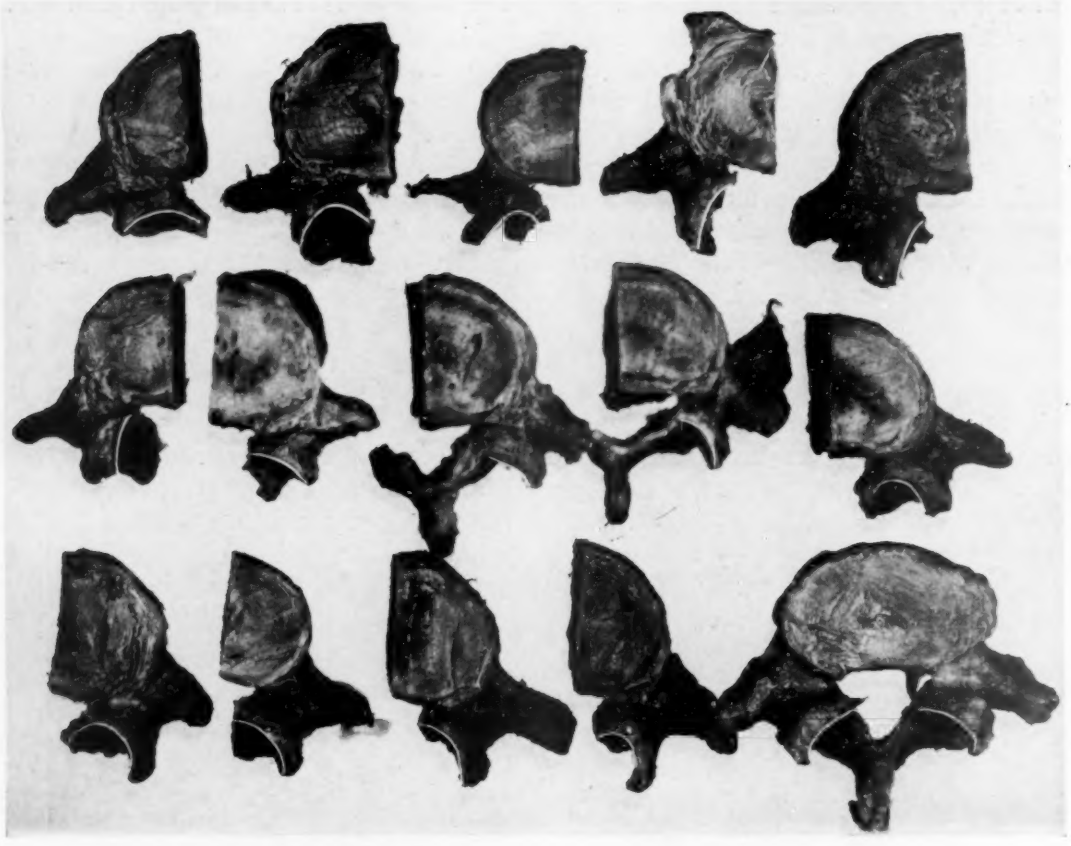

Fig. 3. Superior facets of fourth lumbar vertebra. There is wide variation in the shape of the articular surfaces of the facets, from flat to markedly concave; the angle of the plane of these surfaces varies from the coronal to the sagittal planes.

eration of the vertebral bodies, which is usually most advanced anterolaterally; and it is an additional method in diagnosing impingement of the fifth lumbar transverse process against the sacrum or ilium.

II. Studies of the Articular Facets and Apophyseal Joint Spaces

Since the articular surfaces of the facets of the cervical vertebrae are flat, and are at right angles to the sagittal plane of the body, they are visualized clearly on the direct lateral view roentgenogram of the cervical spine. The facets between the atlas and epistropheus converge so that the inferior facets of the first cervical vertebra look downward and medialward, and are visualized on the anteroposterior view through the open mouth (Fig. 1).

In the thoracic region the articular facets are flat, almost vertical and are placed at an angle of 70° to the horizontal plane. They are roentgenographed with the patient lying in the prone-lateral position on the side of the facets to be studied, the opposite side of the breast being raised to an angle of 70° from the table (Fig. 1).

In the lumbar vertebrae and in the inferior facets of the twelfth dorsal vertebra, the axis of the plane of the facets, which are vertical, is rotated backwards at an angle of 45° so that the superior articular process looks dorsalward and medialward, and the inferior ventralward and lateralward. To visualize them roentgenographically, it is advised that the patient lie in the supine-lateral position, on the side in which the facets are to be roentgenographed, with

the opposite side raised to an angle of 45° from the table (Fig. 1).

In our study, the lumbar and lumbosacral facets and the zygapophyseal joints were investigated in 80 lumbar spines and pelves, 76 male and 4 female, 44 colored and 36 white. An analysis of Table 1 shows that while the lumbosacral facets (5L-1S) are usually flat (85.9 per cent), in 14.1 per cent the superior facet of the first sacral vertebra is concave, and the inferior facet of the fifth lumbar vertebra is convex; that the incidence of this latter relation increases in the upper lumbar vertebrae, 49.2 per cent between the fourth and fifth; 80.7 per cent between the third and fourth; 78.8 per cent between the second and third; and 100 per cent between the first and second lumbar vertebrae (Figs. 2–5). This curvature of the articular surfaces, since penetration of the roentgen rays in a plane parallel to the joint surfaces is impossible, will produce on the roentgenogram a summation of shadows which may falsely give the impression of changes in the clarity and width of the joint space or of increased density of the adjacent bone.

In addition, the zygapophyseal joint space and the surrounding structures will be accurately visualized only if the planes of the articular facets, even if they are flat, are the same or almost the same as that of the oblique projection of the roentgenogram (i.e., 45°). The facets and zygapophyseal joint spaces between 5L-1S in 56 per cent, between 4L-5L in 34.3 per cent, between 3L-4L in 60.7 per cent, between 2L-3L in 89.1 per cent and between 1L-2L in 100 per cent of our specimens, would not have been accurately visualized by a 45° oblique view of the lumbar spine (Table 1). The true lateral view visualizes those facets and joint spaces in the coronal plane, and the anteroposterior view, those in or almost in the sagittal plane. The possible value of additional 60° and 30° oblique

TABLE I

ANALYSIS OF A STUDY OF THE APOPHYSEAL JOINTS AND ARTICULAR FACETS IN 80 LUMBAR SPINES AND PELVES

Articular processes between		5L-1S	4L-5L	3L-4L	2L-3L	1L-2L
No. of lumbar spines dissected		80	80	73	40	11
Angle of axis of apophyseal joint space, as measured from the sagittal plane (figures in per cent)	Symmetrical	63.2	78.9	81.7	82.1	80.0
	Asymmetrical	36.8	21.1	18.3	17.9	20.0
	90°	5.0	2.2	—	—	—
	75°	5.0	1.1	—	—	—
	60°	26.0	22.2	3.6	—	—
	45°	44.0	65.7	33.3	10.9	—
	30°	9.0	4.4	22.1	34.8	25.0
	15°	6.0	2.2	20.3	30.4	50.0
	0°	5.0	2.2	10.7	23.9	25.0
Shape of articular surfaces (figures in per cent)	Symmetrical	76.3	75.0	78.7	73.1	71.4
	Asymmetrical	23.7	25.0	21.3	26.9	28.6
	Flat	85.9	50.8	19.3	21.2	44.4
	Concave-convex	14.1	49.2	80.7	78.8	55.6
Bilateral fusion of apophyseal joints		1	1	1	1	1

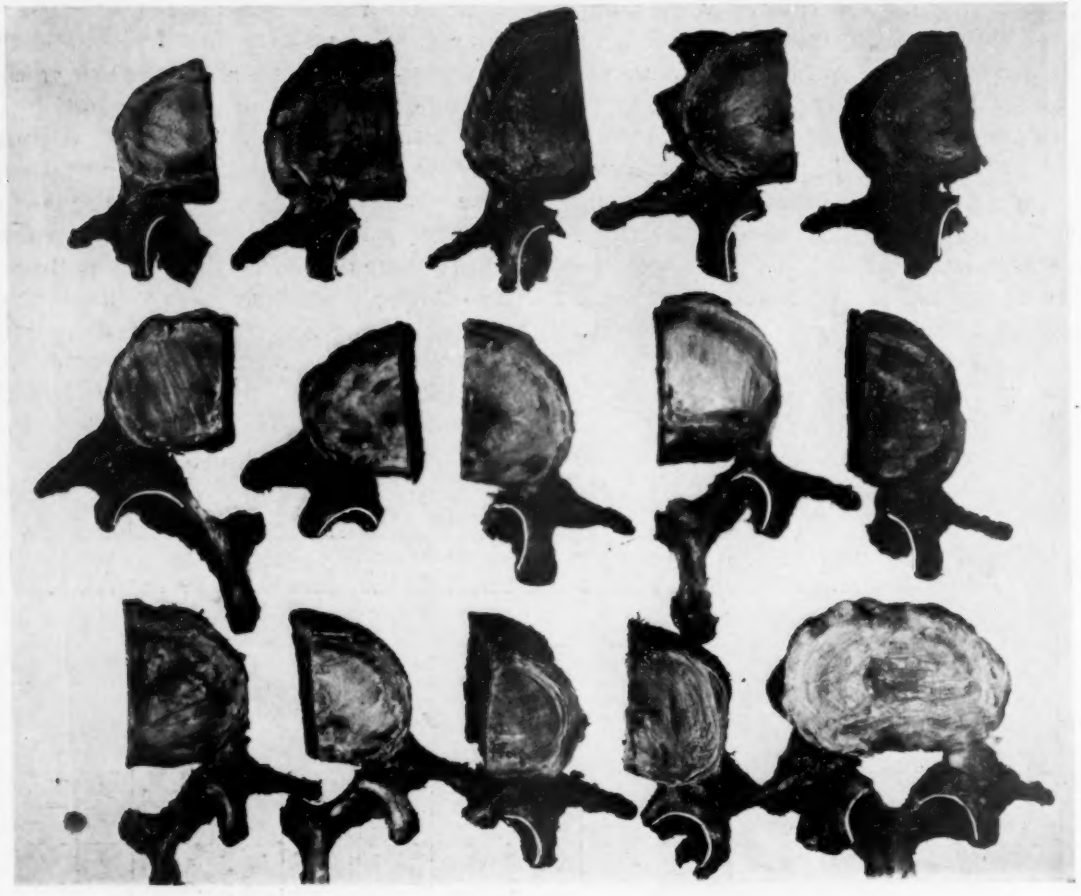

FIG. 4. Superior facets of the fifth lumbar vertebra. There is wide variation in the shape of the articular surfaces and in the angle of these surfaces from the sagittal plane of the vertebrae. There is "tropism" of the superior facets in the complete vertebra illustrated at the right end of the lowest row of specimens.

views of the lumbar spine, when the 45° views are suspicious of pathological change in the facets and their joint spaces, is suggested by the wide variance normally present in the plane of axis of these joints (Figs. 2–5).

Degeneration of the cartilage of the articular processes with marginal bony proliferation and capsular thickening and occasionally ankylosis was present in 31 per cent of the 80 specimens. Such changes were most advanced in the zygapophyseal joints between the third and fourth and between the fourth and fifth lumbar vertebrae and were less marked in the lumbosacral facets, findings which are in keeping with those of Putti and Logroscino[34] in their study of 75 spinal columns.

"Tropism" of the lumbosacral facets, i.e., the plane of the articular processes being coronal on one side and sagittal on the other, was found in 8 specimens and was associated in all with advanced degenerative changes in the adjacent vertebrae, intervertebral joints and cartilaginous discs. Similar advanced changes were found in 7 out of 8 specimens where the facets were bilaterally placed in the sagittal plane. Where the facets were in the more stable coronal plane (7 specimens) such advanced changes were seen in only three.

The posterior margin of the fourth lumbar vertebra extended posterior to that of the fifth lumbar vertebra for a distance of $\frac{1}{8}$ to $\frac{1}{4}$ of an inch in 9 specimens, and was associated in each instance with marked

degenerative changes in the lumbosacral intervertebral disc and with marginal bony proliferation. In no instance was a defect noted in the neural arch, accessory processes or vertebral body. In only one instance were the planes of the lumbosacral facets less than 45° from the sagittal plane of the body; a fact at variance with the teachings of Ferguson[10] and others[18,20,22,41] who have discussed the diagnosis of "posterior spondylolisthesis" and its rôle in the etiology of backache.

III. ACCESSORY ARTICULAR PROCESSES

These processes are described as instances of ununited accessory epiphyses by a number of authors (Nichols and Shiflett,[28] Fulton and Kalbfleisch,[11] Rendich and Westing[35]). Their occurrence is not unusual in the light of the frequency of occurrence of ununited secondary centers of ossification at the tips of the spinous and transverse processes. McMurrich,[24] in describing the appearance of the vertebral secondary centers of ossification at puberty, notes that "in the lumbar vertebrae, others appear at the tips of the articulating processes." Bailey[2] believes that such fissures across the vertical articular process are formed more commonly by the presence of ununited accessory centers of ossification, and are to be differentiated from fractures. Of the 5 cases of "isolated fractures of the articular processes of the lumbar vertebrae" reported by Mitchell,[26] 3 in which the lesion was bilateral and unassociated with a history of trauma probably represent cases of ununited accessory epiphyses. Bailey collected 19 cases from the literature, 6 of these bilateral, and added 10 of his own, one bilateral. All involved the inferior articular processes, except one which occurred in the right superior articular process of the third lumbar vertebra.

In our investigation of 100 adult lumbar spines, there were accessory facets, uni-

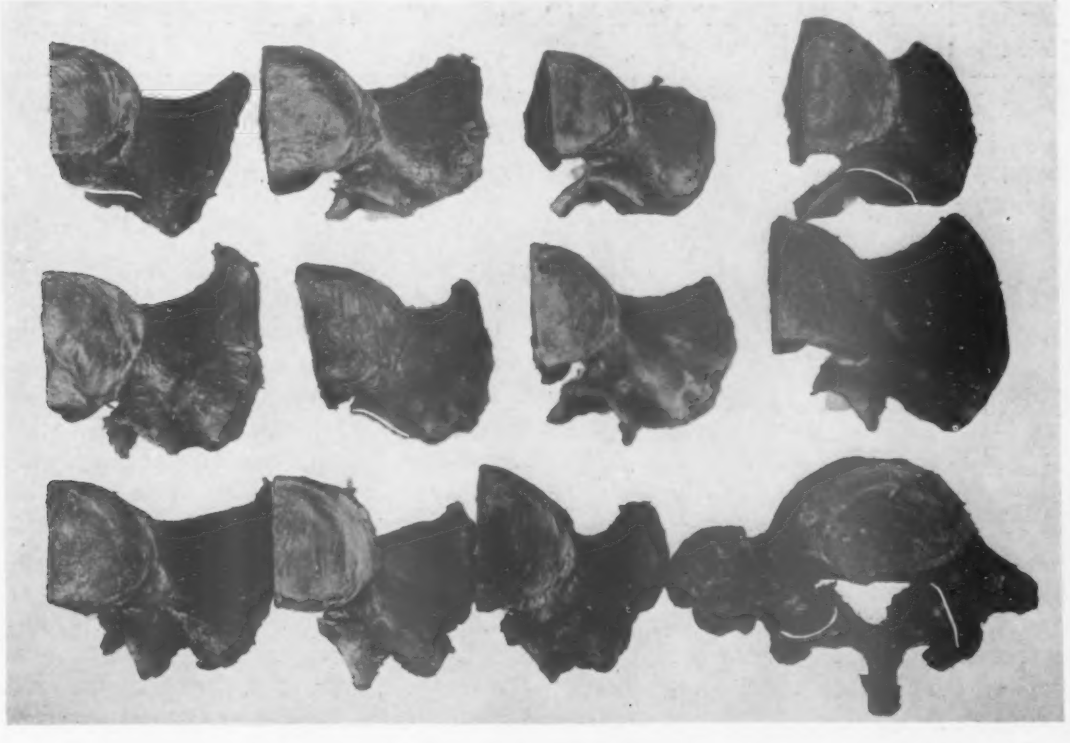

Fig. 5. Superior facets of the first sacral vertebra. There is wide variation in the shape of the articular surfaces and in their angle from the sagittal plane of the vertebrae. There is "tropism" of the inferior facets of the fifth lumbar vertebra illustrated at the right end of the lowest row of specimens.

lateral or bilateral, single or multiple, in 14. The protocols of these specimens were reviewed and in no instance was there a history of severe trauma to the lower spine. In many, a smooth cartilaginous surface lined the opposing fragments, but occasionally only fibrous tissue was found interposed. In 2 of these specimens, there was an anterior displacement of the fifth lumbar vertebra on the sacrum, associated with a bilateral pedicle defect in the fifth lumbar vertebra (anterior spondylolisthesis). The accessory ossicles occurred at the tips of the superior facets in 4 specimens, and involved the tips of the inferior facets in seven (Table II).

TABLE II

Vertebra		L_3	L_4		L_5		1S
Articular facet		Inf.	Sup.	Inf.	Sup.	Inf.	Sup.
Unilateral	Right	1		1	1		1
	Left	1	1	1		1	
Bilateral						2	1

There were multiple occurrences of these accessory processes within the same specimen, in 3 lumbar spines:

1. L_5-inferior facet-bilateral
   L_5-superior facet-bilateral
   L_4-superior facet-bilateral
2. L_5-inferior facet-bilateral
   L_5-superior facet-unilateral (left)
   L_4-inferior facet-unilateral (right)
3. L_5-inferior facet-bilateral
   L_4-inferior facet-unilateral (left)
   L_4-superior facet-bilateral

IV. ROENTGEN DIAGNOSIS OF INTERVERTEBRAL DISC HERNIATIONS INTO THE VERTEBRAL BODY

Snure and Maner[42] in a study of the roentgen appearance of metastatic malignancy of bone noted that spongiosa occupying an area of 2×2.5×2.75 cm. and 1 cm. deep could be removed and replaced by paraffin, without roentgen evidence of a defect. They call attention to the work of Böhmig and Prévot,[4] who in 37 per cent of proved autopsy specimens found no roentgen evidence of intervertebral disc herniations. Chasin[7] produced artificial defects in the vertebral column, as well as in the bones of the hip and knee joints, in an effort to demonstrate the limitations of roentgenology as a diagnostic measure. Lachmann,[23] after studying more than 190 artificially produced defects of varying size and location in the bones of the knee joint, found that conoid shaped excavations involving only the cancellous bone required a diameter of 0.75 to 1.75 cm. at their base and a depth of 0.5 to 2 cm. before they could be visualized on the roentgenogram. Wagoner,[44] by immersing vertebrae in water to simulate body tissue opacities, found that a defect in the spongiosa of 4×6×9 mm. size had properties permitting accurate diagnostic possibilities by the roentgen ray. Similarly, the absence of roentgenographic evidence in certain metastatic malignant lesions of the osteolytic variety in the vertebral column has been noted by Simpson,[40] Kaufmann,[21] Grausman and Sutro,[14] and others, the defect becoming visible only when it is large enough to produce a definite contrasting shadow, or when osteosclerosis occurs in the surrounding tissues.

In our studies two vertebral bodies were sectioned in the sagittal plane and numerous cavities created in the spongiosa, measuring from 2 to 6 mm. in diameter, and these were filled with intervertebral disc material. These specimens were roentgenographed but in no instance could any

defect be definitely visualized (Fig. 6).

Interest in the histologic characteristics of intervertebral disc herniations was initiated by the writings of Schmorl[38] and supplemented by the contributions of Beadle,[3] Calvé and Galland,[6] Sashin,[37] Compere and Keyes,[8] and others. They noted that the nuclear material is extruded through a crack or other defect in the cartilage plate into the spongy bone and becomes transformed into a cartilage nodule. A reaction of the adjacent bone is set up as a secondary line of defense against the invading disc material. It is only after this zone of bony sclerosis and increased calcification appears that the herniation becomes evident roentgenographically.

There are therefore several factors which determine the visibility of a bony defect in the roentgenogram:

1. State of calcification or trabecular condensation of the surrounding bone.
2. Content of the defect.
3. Relative amounts of cortical and spongy bone overlying the defect.
4. Diameter of the transradiated bone which is superimposed over the defect.
5. Distance of the defect from the tube and from the film.

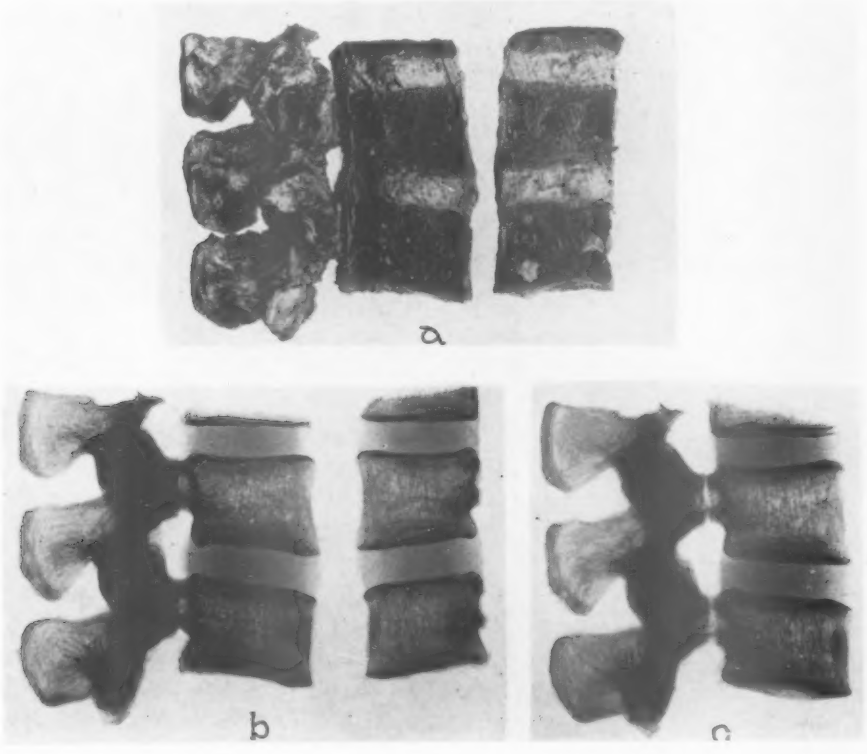

Fig. 6. *a*, numerous defects, measuring from 2 to 6 mm. in diameter, have been created in the spongiosa of two lumbar vertebrae, and these have been filled with intervertebral disc material (as shown in the lower vertebra). Roentgenograms of both sagittal sections, separately, *b*, and together, *c*, fail to visualize any demonstrable defects.

6. Direction of the longest axis of the defect in relation to the central roentgen-ray beam.

V. Anatomical, Pathological and Roentgenological Observations on the Sacroiliac Joint

The articular portion of the sacroiliac joint is of the diarthrodial type. Sashin[36] noted the features of a true diarthrodial joint in all human sacroiliac joints up to

the age of thirty (43 subjects). We obtained the same impression from those specimens in our series in which degenerative changes had not yet appeared. We believe that the frequent occurrence of pathological changes in the sacroiliac joint above the age of thirty may explain why some anatomists have described this articulation as an amphiarthrosis. The anterior sacroiliac ligament is relatively weak and is easily torn by distracting the innominate bones after dividing the symphysis pubis. The posterior sacroiliac ligaments, consisting of the long, short and interosseous ligaments, and the accessory sacroiliac ligaments (sacrotuberous and sacrospinous) are essential in supporting the sacrum as it lies slung between the iliac bones, bearing the rôle of keystone of an arch and transmitting the weight of the trunk to the lower extremities. Reciprocal sinuosities, tubercles and depressions, permit an interlocking of the articular and nonarticular surfaces. Anteriorly the joint resembles an S, being concave inwards above the innominate line, and concave outwards below this line. Testut,[43] disagreeing with most other anatomists, measured 10 sacrums in their superior, middle and inferior planes and concluded that the width between the margins of both sacroiliac articular surfaces dorsally exceeded the corresponding anterior measurements in all planes, especially the middle.

Measurements on 28 macerated sacra, herein recorded, coincide in great part with those made by Testut (Table III).

In the upper part of the articular surface of the sacrum the distance between the anterior margins of the articular surfaces is consistently less than the measurement between the corresponding points on the posterior articular margins. Although a transection of the sacrum in its upper level is shaped like a cone with its base on the ventral (pelvic) side and offers an unstable mechanism against the shearing forces from above, the sudden deviation of the articular surfaces toward the midline anteriorly, therefore, creates a factor of mechanical safety. Further stability is added by the alternating variations between the ventral (pelvic) and dorsal measurements in the various horizontal planes of the sacroiliac joint, the dorsal measurements exceeding the ventral in a mid-transection, and the ventral exceeding the dorsal measurements in a low transection. In a plane at the lowest portion of the sacroiliac joints the dorsal measurements again exceed the ventral measurements (Fig. 7).

With deficient bony mechanical strength in the upper region of the sacroiliac articulation, where much of the superincumbent weight is transmitted due to the almost horizontal position of the human sacrum, much depends on the posterior sacroiliac ligamentous structures. It is not unusual that pathologic changes should become evident first or advance more rapidly in the

TABLE III

MEAN MEASUREMENTS BETWEEN THE SACROILIAC JOINT SURFACES IN 28 SPECIMENS

(Extent of variation in parenthesis)

	Anterior	Posterior
Upper plane of sacroiliac joint	9.93 cm. (8.2–11.1) (11.29 cm. (10.2–11.7) is distance between the joint surfaces just behind the anterior margins)	10.47 cm. (9.0–11.4)
Middle plane	9.01 cm. (8.1– 9.9)	9.41 cm. (8.3–10.8)
Lower plane	9.78 cm. (8.1–10.2)	8.49 cm. (7.5– 9.6)

upper portion of the joint. Brooke,[5] in a study of 200 anatomical specimens, found ankylosis of the sacroiliac joint in 37 per cent of 75 male specimens and none in the female specimens. Sashin[36] in 257 fresh and macerated pelves found progressively advancing degenerative changes in the sacroiliac joints above the age of thirty. Bony ankylosis was noted in 57 per cent of male and 5.8 per cent of female sacroiliac joints seen in 37 specimens, and ankylosis of the sacroiliac joint was present in 21 specimens, all male. As observed, also, by Schunke,[39] changes were noted first, or were found more advanced in the posterior portion of the anterosuperior part of the capsule and anterior sacroiliac ligaments, with exostosis formation followed by complete bony bridging (Fig. 8). In the more advanced specimens this bony ankylosis

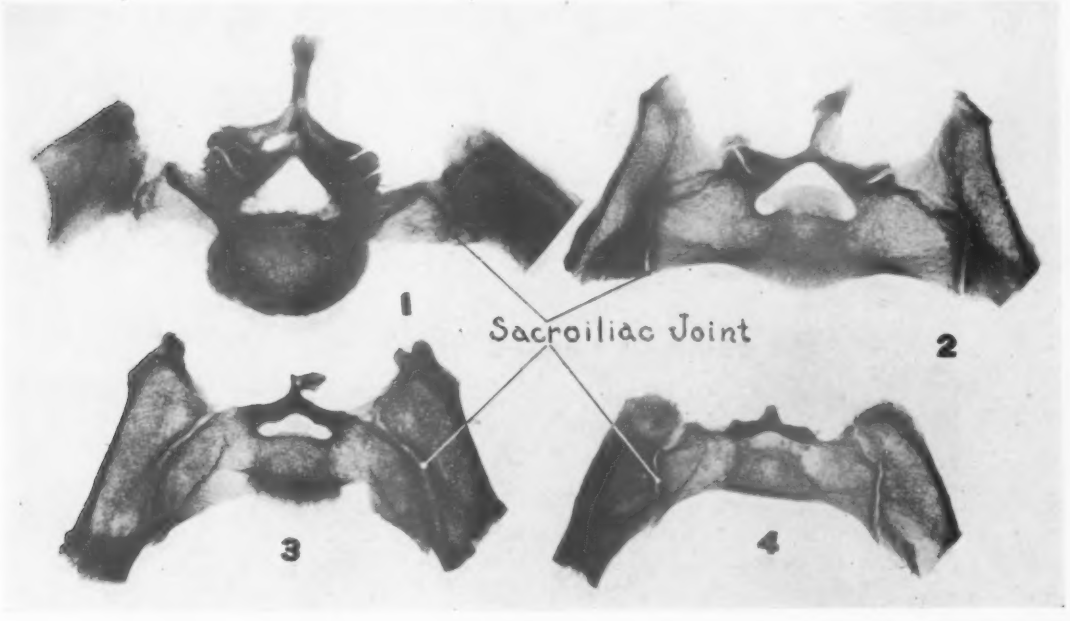

Fig. 7. Transections through the sacroiliac joints in the upper *1*, middle *2*, and lower *4*, planes and in a plane, *3*, midway between *2* and *4*. The regularity and the direction of the plane of the joint cavities vary widely in these different levels. A 45° oblique roentgenogram would have clearly visualized only the uppermost portions of these articulations.

between the ages of thirty and fifty-nine, and in 82 per cent of male and 30 per cent of female sacroiliac joints above the age of sixty. Schunke[39] noted that partial bony ankylosis of the sacroiliac joint was common after the fifth decade, especially in males, and found extra-articular ankylosis in 9 out of 21 adult bodies, bilaterally in seven.

This study comprises an analysis of 100 human pelves (200 sacroiliac joints) of which 94 were male, 6 female, 54 black and 46 white. Degenerative changes, consisting of fibrillation of the articular cartilage and marginal bony proliferation, were extended downwards, invading the joint cavity until complete fusion of the joint surfaces was present. The frequent occurrence of extra-articular ossification superiorly, or synostosis of the superior portion of the sacroiliac joint, with the remaining portions of the joint intact, was a striking observation. Ankylosis of the entire articulation was present in 16 specimens and partial ankylosis in 15, a total occurrence of 31 ankylosed sacroiliac joints (15.5 per cent); occurring bilaterally in 10, more advanced on the right side in 5 and on the left side in 5, and unilaterally in 11, 4 on the right side and 7 on the left.

The variations and irregularities in the contour of the articular surface of the sacroiliac joint, and the deviations in the plane of the joint surface at various levels of the joint in the same specimen and in different specimens, indicates that no one roentgenographic projection may be depended upon for its accurate visualization. For example, the upper part of the joint was visualized clearly on the roentgenogram in only 6 out of 28 normal sacroiliac joints by means of the 45° oblique view. The results of diagnosis of partial and complete fusion in this articulation, even with careful stereoscopic views, is disconcerting. In the comparative anatomical and roentgenographic analysis of 25 lumbar spines and pelves previously mentioned, this diagnosis was correctly made on the roentgenogram in 6 specimens; in 4, synostosis was apparent on the roentgenogram but was not present in the gross specimen; while in 1, fusion of the joint was present in the gross specimen, yet the articulation appeared intact roentgenographically.

FIG. 8. Early synostosis of the left sacroiliac joint; extra-articular ankylosis involves the capsule and anterior sacroiliac ligaments in the posterior-superior part of the articulation, *X*, while the remaining portions of the joint are intact.

CONCLUSIONS

The roentgenographic study of the lumbar spine and pelvis must be interpreted and evaluated with care. Limitation in the value of the oblique projection is suggested following comparative anatomical, pathological, and roentgenological studies on 25 human lumbar spines and pelves, and is explained following anatomical and pathological observations of the articular facets and apophyseal (intervertebral) joints of the lumbar spine and the sacroiliac joints in 100 human cadavers.

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DIAGNOSTIC PROBLEMS IN SURGERY OF THE UPPER URINARY TRACT*

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IN THE urologic practice of today very few cases are not diagnosed correctly, making an exploratory operation a procedure of the past. We have means today not only to diagnose the anatomic phase of the upper urinary organs but also to visualize their physiologic mechanism in action, whether normal or abnormal. Intravenous urography has placed a most valuable method at the disposal of the profession at large and has freed the patient from the hesitancy and fear of an instrumental study.

Intravenous urography is gradually moving into the combined province of the practitioner of medicine and the roentgenologist. It is gratifying to note the alertness and care with which the technique and interpretations are carried out today. This special effort is undoubtedly due to the great responsibility felt by the roentgenologist in doing intravenous urography. He is conscious of the fact that success or failure depends upon proper diagnosis by urographic interpretation. The responsibility is felt even more when normality is to be diagnosed and pathology excluded. Often it takes more study and more care to prove a normal status of the urinary tract, than in complicated pathology.

We always ask for the repetition of this study whenever a doubtful point is at issue. It is much safer to do so than to dismiss it, since a single, often unimportant point, not completely answered, may be the main clue to the proper diagnosis.

We encounter many instances in which, after having exhausted the diagnostic means at our disposal, we are still confronted with the problems of the correct diagnosis. The classical symptomatology is not always present. There may be a tumor without blood and a pyonephrosis without pus in the urine. A patient may have a renal colic without a stone and a stone without a colic.

CYSTOSCOPY BEFORE UROGRAPHY IN HEMATURIA

While urography is the procedure of choice whenever a urological complaint is present, it is otherwise in hematuria. Here cystoscopy should precede urography in order to ascertain the exact source of bleeding. Most of the hematuric attacks are of short duration and often far apart. If the bleeding has stopped and unless there is frank pathology demonstrable, one is uncertain as to the correct diagnosis. We see such a condition quite frequently, especially in bleeding from the prostate gland. If the upper tract is found to be normal, it is assumed that the bleeding came from the prostate. This, however, may be erroneous and leaves one without a definite diagnosis.

There is no medical contraindication to cystoscopy during the bleeding stage. The still prevalent idea of waiting until the bleeding has stopped is fallacious and dangerous.

ABDOMINAL AND RENAL PATHOLOGIES MASKING ONE ANOTHER

There are many instances of abdominal symptoms masking true renal disease, and vice versa, the renal symptomatology obscuring the true abdominal disease. We saw a patient with bilateral renal stones; a stone was removed from the left kidney while the suspected stone of the right kidney turned out to be a gallstone (Fig. 1).

* From the Urological Service of the Mt. Sinai Hospital and the School of Medicine, University of Pennsylvania. Read before the Philadelphia Roentgen Ray Society, April 6, 1939.

There was another instance of renal stone in which, because of a few mottled spots on the pelvic bones, a malignant condition was suggested. Some vague abdominal pain was attributed to the renal calculus for which we treated the patient for the existence of the gastric carcinoma was not suspected by the nephew of the patient, a very careful gastroenterologist. The few gastric symptoms of occasional nausea and eructation were attributed to the reflex irritation of the renal calculus.

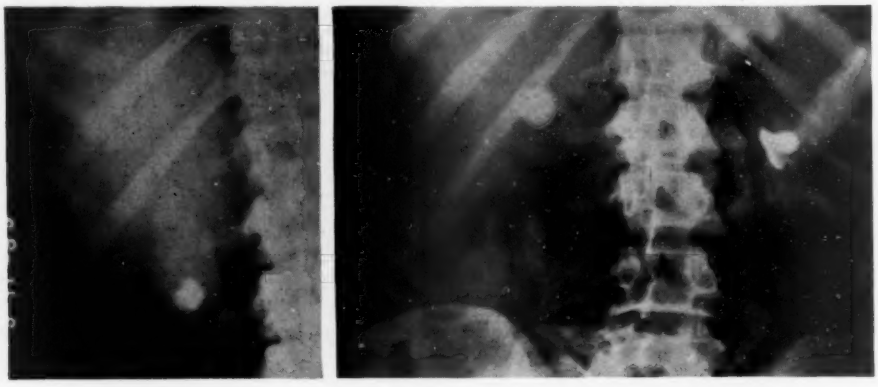


FIG. 1. Bilateral stones. The shadow on the left is renal calculus, the shadow on the right is gallstone.

years. Gastrointestinal study revealed an unsuspected carcinoma of the splenic flexure of the colon (Fig. 2).

We witnessed a similar occurrence in a patient already under anesthesia on the operating table for the removal of a renal calculus. The operation was postponed because of persistent vomiting during ether induction. The vomitus consisted of food ingested twenty-four hours earlier. Gastrointestinal study later revealed an extensive carcinoma of the stomach (Fig. 3). The symptoms in this case were so slight that

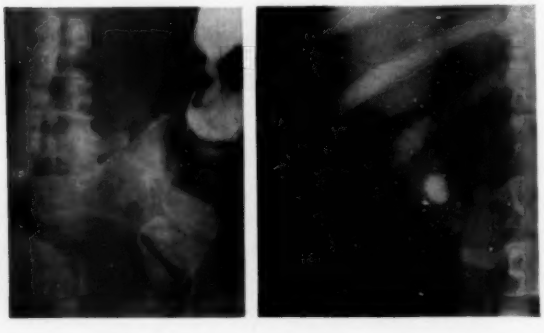


FIG. 2. Abdominal pain ascribed to a renal calculus was found to be due to carcinoma of the splenic flexure of the colon.

In our study of ureteral calculi we found gastrointestinal symptoms in 29 per cent of the cases.

In a typical case of appendicitis being prepared for surgery, the easing of pain made the surgeon hesitant. A markedly ptosed kidney down in the iliac fossa with blockage due to kinking of the ureter was discovered later.

A young boy with backache and fever was treated for kidney disease over a period of several weeks. Complete study revealed congenital bilateral pelvic kidneys; the severe backache was found to be due to a tuberculous spondylitis of the eleventh and twelfth thoracic vertebrae (Fig. 4).

DIFFERENTIAL DIAGNOSIS OF STONE IN THE URETER

The differential diagnosis of stone in the ureter and appendicitis is often very trying. It is a daily occurrence and taxes our ingenuity and sense of responsibility. I am certainly in favor of operating on the appendix whenever in doubt, but it is not such an innocuous procedure in the presence of stone. Although the presence of local tenderness is most significant, we have

seen it masked by the muscular spasm of a rapidly descending stone producing peritoneal irritation, because of the close proximity of the traumatized ureter to the peritoneum. Generally speaking, we believe that whenever the pain is severe a renal block should be suspected.

A patient entered the hospital with abdominal distention, generalized abdominal rigidity and no bowel movement for three days. A tentative diagnosis of intestinal obstruction was made and operation was thought to be imperative. Because of the poor general condition of the patient, the operation was postponed for several hours to give him medical care and Wangensteen drainage. He passed a stone and was promptly and completely relieved of all his symptoms. In a similar case we saw a colostomy done.

Carp, studying the symptomatology of 100 consecutive cases of ureteral calculus from our service, found a normal leukocyte count in only 10 per cent, while in 45 per cent of the cases the count was between 10,000 and 15,000. The evidence of leukocytosis in such a situation is therefore not absolutely indicative of appendicitis.

The classical urinary symptoms of frequency, dysuria, or hematuria may be expected because of the existing stone, and

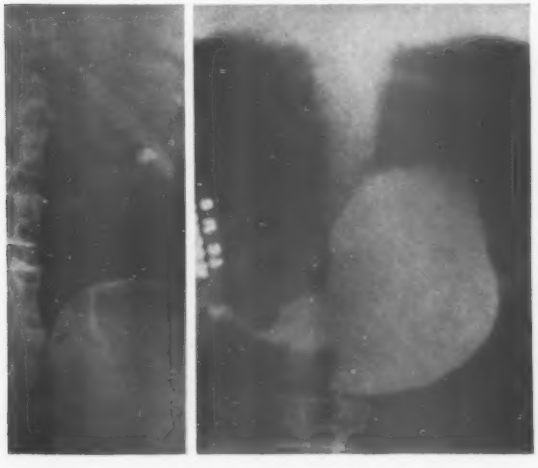


Fig. 3. Case of renal calculus on operating table. Operation deferred because of persistent vomiting during induction of ether anesthesia. Gastric carcinoma discovered later.

Fig. 4. Backache treated for renal disease. Both kidneys in pelvis (congenital). Backache due to tuberculous spondylitis of eleventh and twelfth vertebrae (arrow).

yet it is possible to be misled by their absence and still have a stone lodged in the ureter. It can be said definitely that in most cases of stone in the upper and middle third of the ureter, bladder symptoms are absent or rare. Definite bladder symptoms ensue when the stone has reached the lower third of the ureter.

Stones in the lower end of the ureter are frequently very small and faintly radiopaque and can be discerned only after proper preparation. Very frequently as in cases with a rapidly descending small renal calculus, a "primary calculus" (Randall), the shadow casting property is very low. We have learned not to expect a dense shadow, but to carefully scan the area for an irregular, faintly visible density. If in doubt, the passage of a catheter to the kidney will show whether obstruction with retention in the renal pelvis is actually present. We believe that the percentage of roentgen negative stones depends largely

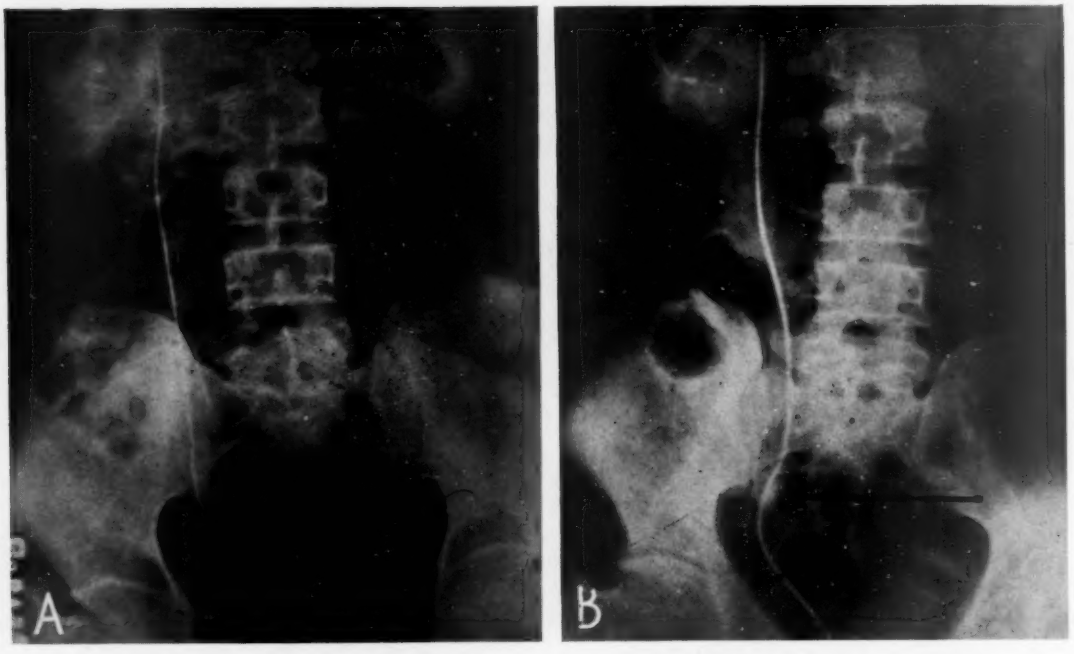


Fig. 5. *A*, stone in lower third of right ureter lying over the sacrum and invisible; *B*, stone visualized by exposure under varied angles, throwing the shadow downward.

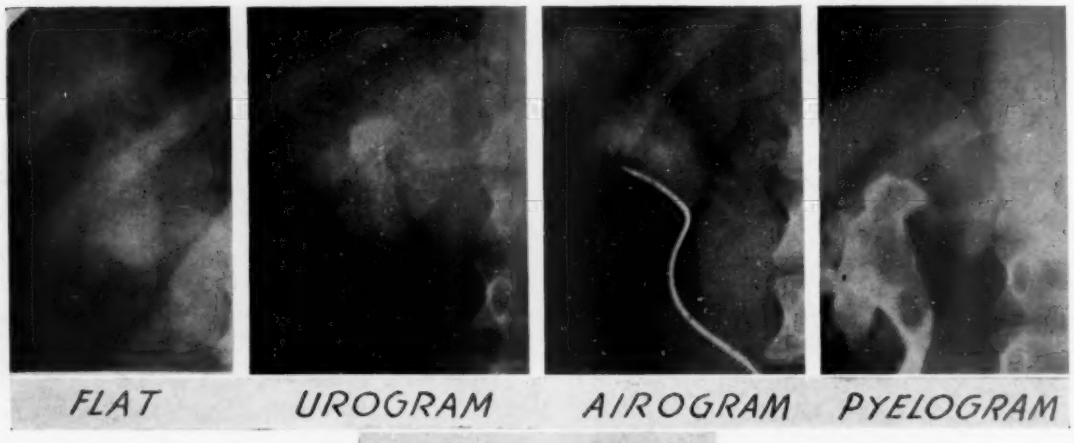


Fig. 6. Visualization of a faint shadow in the renal area by means of urography, pyelography and air injection. Large stone removed.

upon the care with which films are made and studied. In our series of ureteral stones we found only 8 per cent non-opaque and 92 per cent casting a visible shadow.

Stones can be hidden by adjacent opaque structures, the ilium, the sacrum and the transverse processes of the vertebrae. These shadows should be carefully scanned for densities, as a stone overlying them can thus easily be overlooked. If there is a suspicion of such a density, the taking of several exposures under varied angles will throw the stone shadow away from the bone (Fig. 5).

Renal calculi, because of their age, are usually all radiopaque. Occasionally a case is found with a large renal stone casting a very faint shadow. Air injection into the renal pelvis will outline the faint calculus shadow (Fig. 6).

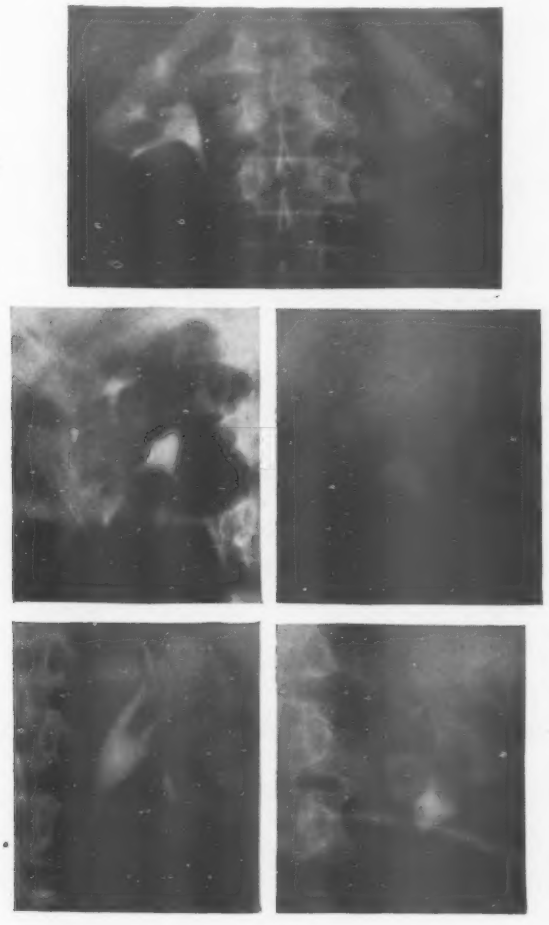


Fig. 7. "Irritable kidney." Spastic states of unknown origin in the normal urogram.

SPASTIC STATES

The regular rhythm of the nervous mechanism of the kidney may be disturbed producing alterations of the normal calyceal and pelvic fillings. This is seen frequently bilaterally, but also unilaterally, one, two or all calyces imcompletely filled producing the effect of a thin spider web. We call it an "irritable kidney," assuming that the propelling mechanism works overtime, not permitting complete filling (Fig. 7).

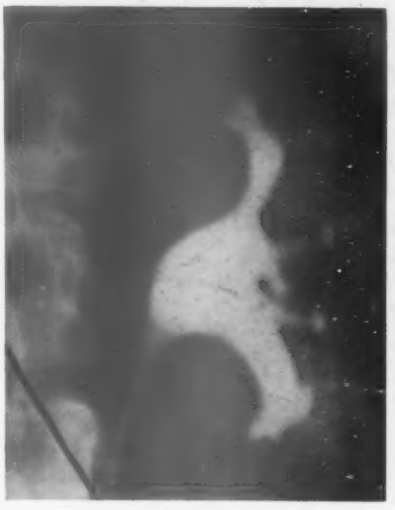


Fig. 8. Spasm of the milking muscle of the renal papillae.

Another phenomenon is observed when the spiral muscles of the calyces become spastic, cutting off a small amount of dye from the continuity of the pelvis. One or several calyces may thus be affected. It is a passing spasm, and may not be found on later studies (Fig. 8).

The pelvis proper may also be affected. We observed on the operating table a case of intermittent spastic contractions of the entire pelvis, appearing every fifteen to twenty seconds. The entire extrarenal pelvis would contract into a small hard ball and disappear within the hilus of the kidney followed by complete relaxation. The

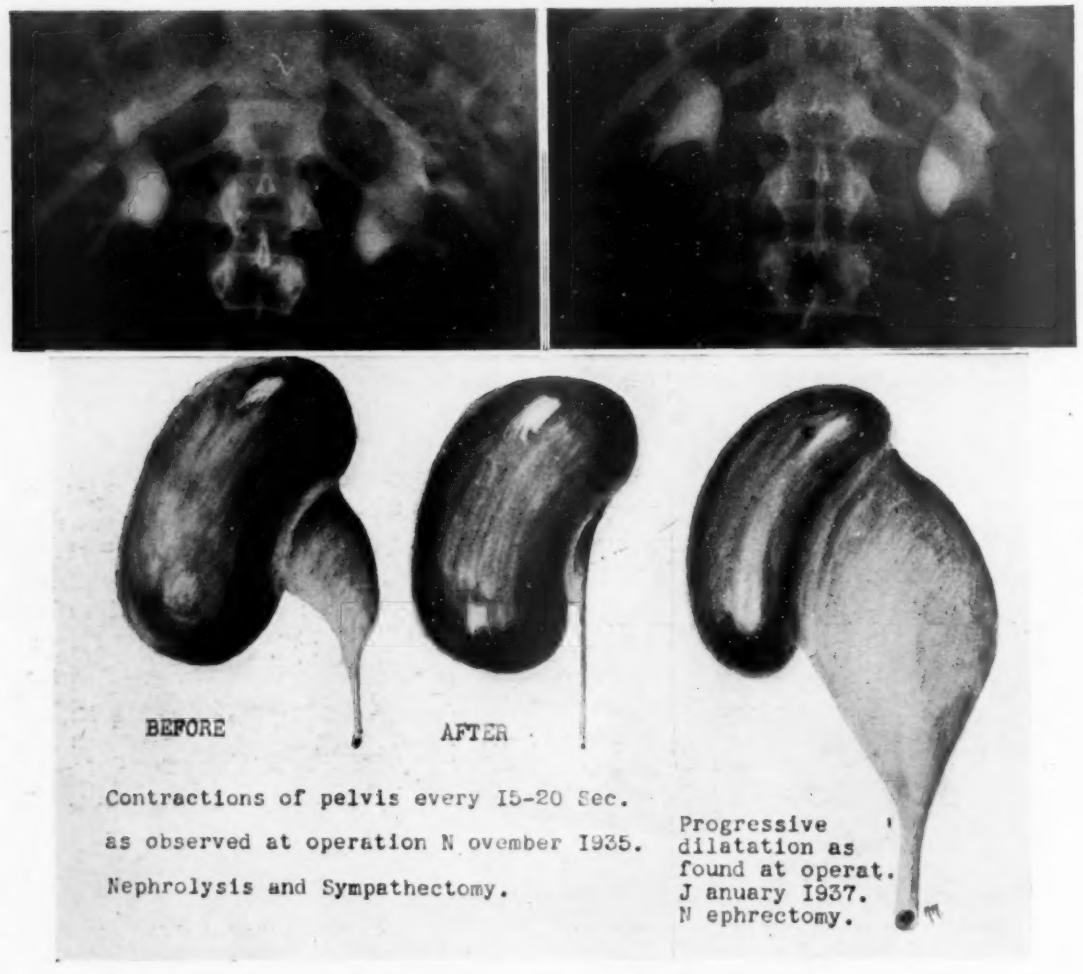


FIG. 9. Spastic contractions of the renal pelvis with varied density of pelvic filling. Powerful contractions of pelvis observed on surgical exposure.

urograms in this case showed varied densities in pelvic filling (Fig. 9).

EMERGENCY UROGRAPHY

There are instances of emergency when one must know definitely whether or not a given kidney is functioning, whether the high fever and severe toxemia are caused by the kidney in question or whether another focus is responsible for it.

This is especially true after operations upon bladder tumor. Randall has shown that in 50 per cent of cases of bladder tumor encroaching upon either ureteral orifice, there is a non-functioning kidney above.

This type of kidney dysfunction is rather unusual. The kidney and pelvic architecture is unchanged or very slightly altered and yet no urine is being secreted. Randall coined the unofficial name of "NRA kidney" (no renal activity) denoting a "sus pended animation." Function is restarted immediately after introduction of a catheter and is continued indefinitely as long as adequate drainage is provided.

In many instances after removal of this catheter, following bladder tumor surgery, there remains a certain amount of edema of the ureteral orifice in the midst of coagulation necrosis with the resulting high fever, chills, and severe toxemia. Reinsertion of the catheter is imperative, but is frequently impossible cystoscopically owing to the

sloughing. Surgical drainage of the kidney is then the only choice. But the fever, chills, and toxemia may also be due primarily to the sloughing of the bladder wall with pericystitis and absorption, denoting inadequate bladder drainage and thus absolving the kidney entirely. We have resorted to intravenous urography in several such emergencies. The finding of a functioning kidney diverts our attention back to the bladder as the causative factor and avoids an unnecessary kidney operation.

RENAL COLIC WITHOUT STONE OR STRICTURE

There are situations in which a typical renal colic is simulated by pathology other than stone or stricture. In the aged who have chronic obstructions at the bladder neck with weakened and dilated ureteral sphincters, there is observed a back pressure colic or "retrograde renal colic" (B. Lewis), which is instantly relieved after the bladder is emptied.

Renal colic without stone is encountered

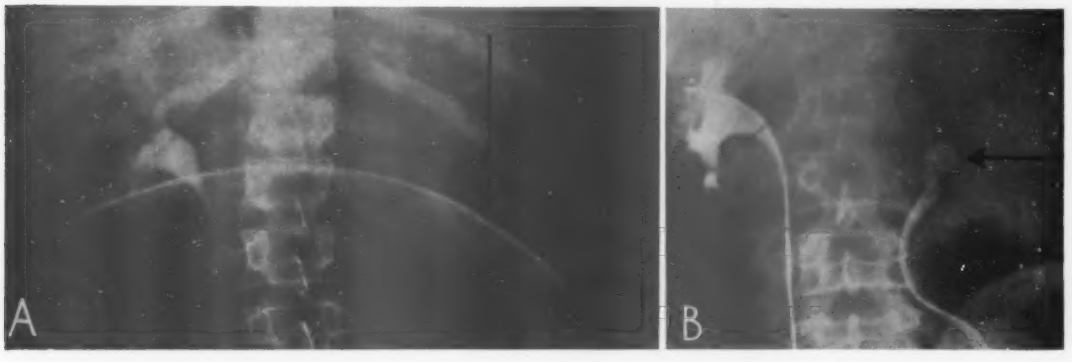


Fig. 10. *A*, huge "silent pyonephrosis"; *B*, ureteral stone with "silent pyonephrosis."

Another emergency where intravenous urography proved of great aid was in a case of an elderly male with high fever and toxemia due to cystitis and bilateral epididymitis. He was complaining of pain in the right upper quadrant anteriorly. Examination showed the pain to be superficial and also on deep pressure. A renal block was suggested. Cystoscopy and catheterization of the right kidney was the only procedure of choice. We feared such a procedure because of the severe grade of infection of the bladder and adnexa, old age and severe toxemia. We resorted to an intravenous urography and were pleasantly surprised to find the kidney functioning well, without evidence of any obstruction. We therefore assumed the pain in the loin to be referred from a severe vasitis especially because of the superficial nature of the pain. The latter course proved this assumption to be correct.

at times in cases of true pelvic and ureteral hypermotility with rhythmic spasms, as previously stated.

Occasionally, severe pain in the loin is seen in fulminant epididymovasitis as described above.

Finally, the presence of a blood clot in the renal pelvis acting as a ball valve with typical renal colic must be considered. It is negative on the roentgenogram, but can be visualized as a filling defect by urography.

STONES WITHOUT COLIC

Only small stones freely movable will produce colic. If a stone is lodged within the ureter over a long period of time, the ureter having become dilated above and the passage of urine being free, no colic is noted. Slow and gradual destruction of the kidney will ensue with the development of a "silent pyonephrosis." Most of these cases present enough clinical evidence to be

easily diagnosed. There is, however, a recognized entity of "silent pyonephrosis" with practically no subjective symptoms, and because of complete blockage of the ureter no pus will be found in the urine. These cases of "silent pyonephrosis" are fever-free and show only a mild leukocytosis. We encountered several such cases in which a stone lodged in the mid-ureter, completely blocking the kidney, with a gradual accumulation of more than 1,000 cc. of thick, foul pus with complete absence of symptoms (Fig. 10). We recall a characteristic case where a patient was treated for a suspected brain lesion, since there was no previous urinary history and the patient in a state of coma showed some cerebral manifestations. Because of a few pus cells in the routine examination of the urine and a previous experience by the physician in attendance, a urological investigation was suggested. A large "silent pyonephrosis" caused by an obstructing ureteral calculus was found and successfully drained, with ultimate recovery.

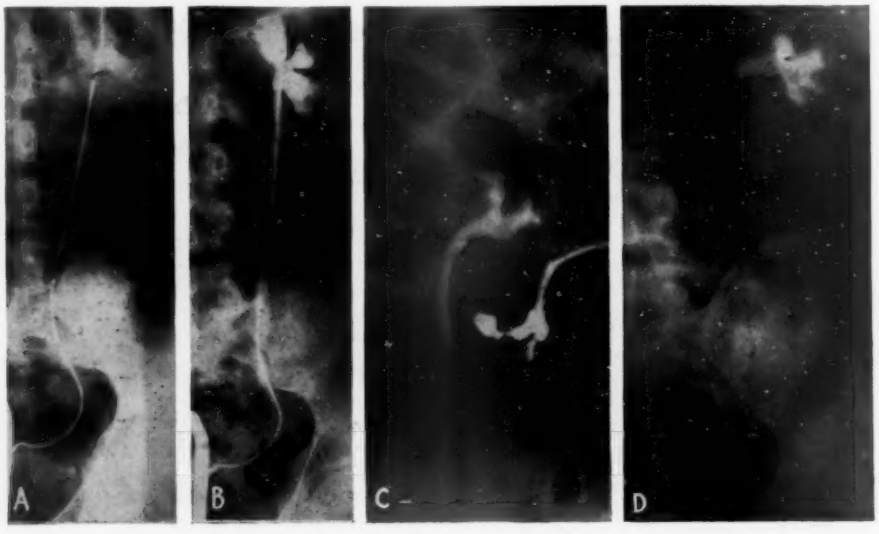


FIG. 11. Persistent renal fistula after nephrolithotomy due to complete occlusion of the calyceal communication with the main pelvis. Before operation: *A*, flat film with stone in lower calyx; *B*, pyelogram. After operation: *C*, pyelography and lipiodol injection into fistula, no filling of lower calyx; *D*, urography fills all calyces.

PERSISTENT RENAL FISTULAE

Renal fistulae after operations may be due to two main causes: extrarenal and renal. The most common extrarenal cause is stone or postoperative constriction of the ureter. We encountered a postoperative fistula with a pyoureter caused by a huge stone within the ureter of long standing. Nephrectomy had been performed years before elsewhere. Vaginal ureterolithotomy brought about prompt closure of the renal fistula.

The cause of the fistula may lie in the kidney itself, as observed by us in one of our cases. We removed a fairly large stone by nephrostomy from the dilated lower calyx, but the fistula refused to close. Careful study revealed no dye in the lower calyx on simultaneous retrograde pyelography and injection of the fistulous tract with lipiodol. Intravenous urography, however, revealed dye secretion within the silent calyx. We therefore assumed that the lower calyx became completely closed off from the main pelvis, acting as a pelvis for itself and draining its urine through the loin fistula. Breaking through the neck of the calyx into the pelvis promptly reëstablishing normal conditions (Fig. 11).

We encountered a third possibility of renal fistula. Following a nephrectomy, the details of which remained obscure, a loin

fistula persisted for years. Intravenous dye appeared through the fistula and at operation we removed a small piece of renal tissue.

PELVIC AND CORTICAL RENAL PAIN

Renal pain is characteristic and is caused by increased pressure within the pelvis due to obstruction. The only sure way to prove that the pain in the loin is renal in origin is by the passage of a catheter into the renal pelvis. This procedure must remove the pressure and will cause instant relief.

In most cases the persistence of pain in the loin, in spite of an indwelling catheter, completely eliminates the kidney as the source of pain. There are, however, exceptions to the rule. We had two such patients in whom pain persisted in spite of the finding of an empty kidney by catheter; at operation we found a subcapsular hemorrhage. We must also think of a sudden increase of pressure within a benign solitary renal cyst or within one of the many cysts in polycystic disease. Pain due to a cortical lesion of the kidney proper will be noted only when the lesion has grown to such an extent as to put the renal capsule under tension.

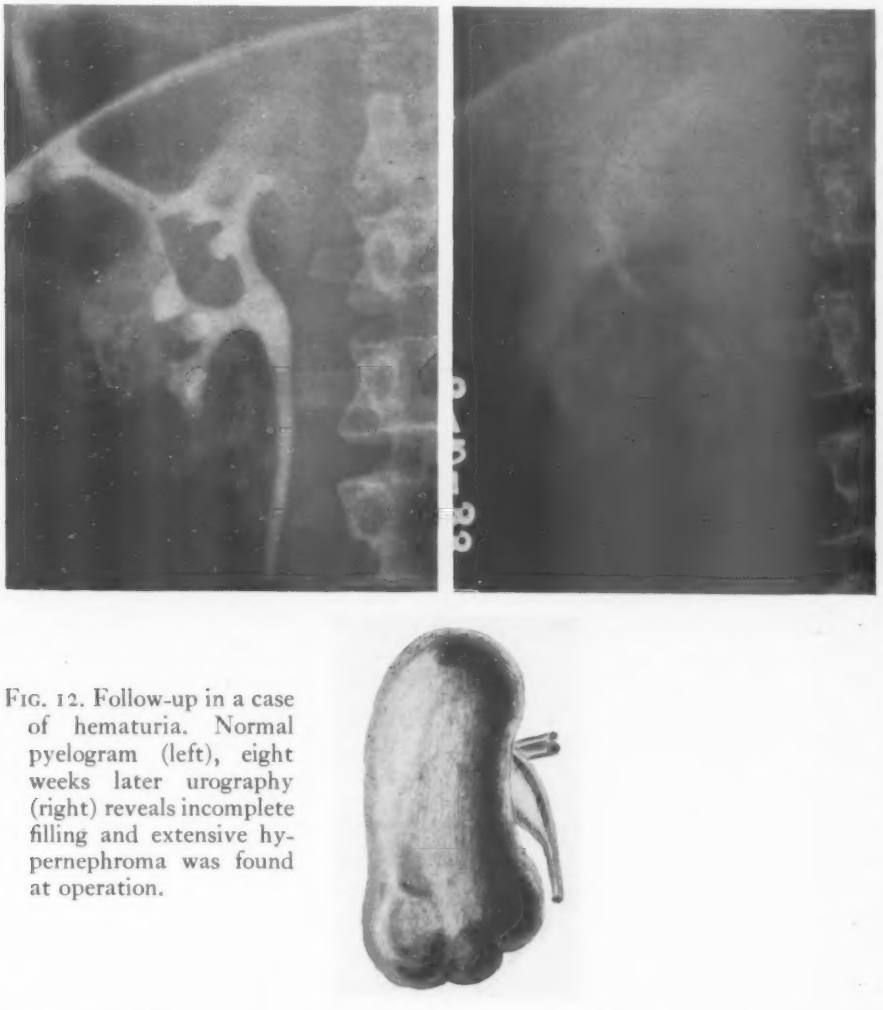


Fig. 12. Follow-up in a case of hematuria. Normal pyelogram (left), eight weeks later urography (right) reveals incomplete filling and extensive hypernephroma was found at operation.

FOLLOW-UP UROGRAPHY

We believe in follow-up urography in all our surgical kidney cases and are either elated about the good results or dismayed about the failures. It enables the use of corrective surgery before it is too late.

Many pathological cases show improvement or regression very rapidly, others rather slowly. Thus we observed an unbelievably rapid infiltration of a kidney with hypernephroma within eight weeks (Fig. 12), and, on the other hand, we watched a case of staphylococcus sepsis by repeated urography gradually develop renal carbuncles after two months on one side and after two more months on the other side (Fig. 13).

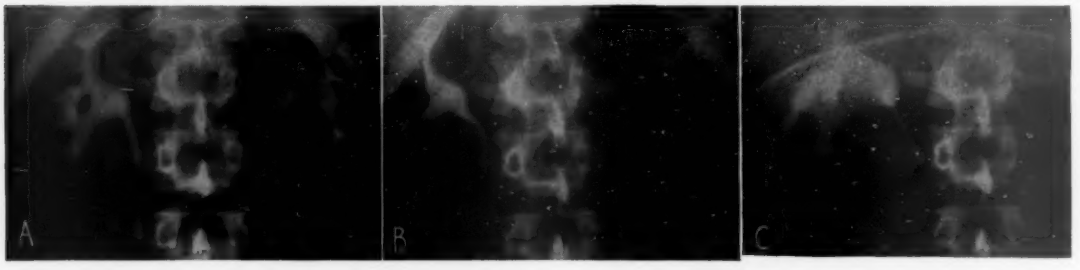
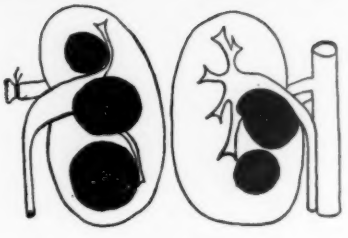


FIG. 13. Follow-up in a case of staphylococcus sepsis. *A*, normal; *B*, two months later, incomplete filling of the right kidney. Operation: Several larger carbuncles, nephrectomy. *C*, four months since normal urogram. Bulging of lower pole with displacement of ureter inward. Operation: huge liquefied carbuncles, drainage with complete recovery.



GRAVE RENAL DISEASE WITH FEW SYMPTOMS

The symptoms in many cases of well advanced grave renal disease are few and often insignificant. We saw a child four years old with a congenital ureterocele of the bladder intermittently blocking both ureteral and urethral orifices, both kidneys having been completely reduced to thin shells with the capacity of a pint each, yet the only complaints were inability to gain weight and a slight pyuria. Although the phenolsulphonphthalein test was zero,there was enough renal tissue left to maintain life, as the blood urea nitrogen was still normal.

In another case, that of a man, aged seventy, with frequency of urination due to a benign enlargement of the prostate, while doing a cystogram an immense renal shell was found occupying the entire abdomen, pushing the intestines to the upper corner of the opposite side. This hydronephrotic bag held more than 3,000 cc. of urine without causing any symptoms whatsoever.

COMMENT

We have attempted to show that we still have, and always will have diagnostic problems in surgery of the upper urinary tract. Refinement of technique and intelligent interpretation of intravenous urography will lead to better surgical results in urology. But this is only possible when not only cooperation but also a special interest exists between the urological clinician and the roentgenologist in the search of a prompt, clear and complete solution of every problem presenting itself.

I want to thank Dr. Louis Edeiken for his intense interest, constant cooperation, and untiring efforts to bring out the many details which solved many of our difficult diagnostic problems.

CONCLUSIONS

1. Intravenous urography has placed renal diagnosis in the hands of the general practitioner and the roentgenologist.
2. Constant cooperation between the urologist and roentgenologist is necesary for detailed study of surgical cases.

3. In hematuria immediate localization of the source of bleeding by cystoscopy is imperative, to be followed by urography later.

4. A thorough examination should precede every surgical kidney case to eliminate coexisting abdominal disease.

5. The high percentage of leukocytosis in ureteral calculus is stressed, especially when diagnosing appendicitis.

6. The poor shadow casting properties of small ureteral calculi and their position behind bony structures is discussed.

7. Renal colic without stone and stone without colic are encountered.

8. "Silent pyonephrosis" is not infrequently seen and is remarkably asymptomatic.

9. Emergency urography is of great value in differential diagnosis of obscure toxemia and fever.

10. Spastic states of the renal musculature are discussed.

11. Rapid and slow progression of renal pathology is demonstrated by follow-up urography.

GASTRODUODENO-COLIC FISTULA: CARCINOMA OF TRANSVERSE COLON

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GASTROCOLIC fistula was first discovered by Murchison.[13] The majority of such fistulas are caused by malignant lesions in the greater curvature of the stomach; the next most frequent cause is a jejunal ulcer developing at the site of a gastroenterostomy stoma. Golob[4] found almost half due to the latter cause. In 21 cases reviewed at the Mayo Clinic 19 occurred after gastroenterostomy and 2 from carcinoma of the colon. Kohlmann[7] adds to the etiologic factors carcinoma of the splenic flexure of the colon, perforation of a duodenal ulcer, tuberculous peritonitis and suppurative cholecystitis. Rees[12] mentions typhoidal ulcer of the colon. Langemeyer[8] describes a case in which gastrojejuno-colic fistula developed after gastroenterostomy and, in trying to work out the pathogenesis, confesses that some of it "bleibt unklar." Peptic ulcers, wherever situated, seem to have this tendency to form sealed communications with adjacent viscera, Moiroud[9] even recounting a case in which the jejunum became fixed to the lesser curvature of the stomach at an ulcer site, taking on thereby some of the characters of a surgical stoma, and markedly ameliorating the patient's symptoms!

Perforation, as described by Morley, Brooke and Little,[10] would seem relatively uncommon.

The diagnosis of gastrocolic fistula, or duodenocolic fistula, or a combination of the two, is more often arrived at roentgenologically than by clinical methods, though there are some fairly constant clinical manifestations.

Diarrhea is the most common and Streicher[13] urges a search for such a fistula in all cases presenting obscure diarrhea. The diarrhea is lienteric in type. One case of night blindness[14]—a deficiency disease and in this case developing in a patient receiving an adequate diet)—was finally found to be due to the food loss resultant upon a gastrocolic fistula. The night blindness disappeared after surgical removal of the fistula. Breitner[1] recorded a case in which the patient developed paresthesias.

When the condition follows gastroenterostomy, eight to nine years has been the average time, though it was only six months in a case described by Polya.[11]

So far as the roentgenologic approach is concerned, the condition shows up much better and much more frequently with a barium enema than following a meal, in the experience of most observers.[4,13] One reason advanced for this is the probable formation of a mucous membrane fold[13] which has a ball-valve action and interferes with the egress of the barium from the stomach.

Very great confusion may arise in the giving of a meal, moreover, as in the case described by Rees,[12] where the passage of barium into the gallbladder from a gastroduodeno-colic fistula was taken merely to be an incompetent sphincter of Oddi. In another case described by Feldman,[3] an enema was altogether misleading, since a fistula from the colon to a kidney was productive only of a filling defect which seemed quite typical of carcinoma (particularly since the patient had a mass in that area). The enema failed of aid in the case of Morley, Brooke and Little[10] because it could not be sent farther than the descending colon. Early, Holzknecht[6] suggested introducing air into the rectum in the hope that it would fill out the "Magenblase."

In the 21 cases described at the Mayo Clinic,[4] the roentgen ray gave positive evidence in 11, doubtful evidence in 1, and was

relatively negative in 8. Diagnosis was made clinically in 9.

REPORT OF CASE

A. J., female, housewife, aged forty-five, of Lithuanian decent. For four and a half months she had complained of weakness, loss of weight, and intractable diarrhea. Food that she ate was passed sometimes in only a few minutes. Her past history, so far as surgery was concerned, was negative.

She entered Cook County Hospital on December 19, 1938, and was sent to the roentgen department on December 27 for barium enema.

As the colon filled, we thought we noticed an irregularity in the transverse colon, close to the hepatic flexure. Its outline was indistinct, and we reserved judgment until we could see the films.

The films showed the stomach distinctly outlined. Though we considered a ball-valve action as one of the possibilities in this delay (for we had seen no stomach outline in the roentgenoscopic room) we were also obliged to consider the possibility of there being a union between the pars descendens of the duodenum and the colon, with no direct connection between stomach and colon.

Fig. 2. Stomach visualized after barium enema.

Fig. 1. Roentgenogram after administration of an opaque meal.

We sent for the patient as soon as the previous barium could be well cleaned out, and this time gave a barium meal. The nature of the communication was by no means distinct as we watched the progress of the meal. The first portion of colon to show an outline was in the region of the splenic flexure. (The lesion, we already knew, was near the hepatic flexure!) We were at length able to demonstrate that the barium was entering near the hepatic flexure and being swiftly carried along to the splenic flexure. An outline of small bowel next became distinct, but only after tedious observation. We could demonstrate no direct connection between stomach and colon. Films showed stomach, small bowel and colon and did not serve greatly to clarify the condition.

The patient went to operation soon thereafter, and the entire region of the hepatic flexure was found encased in a large mass, with omentum drawn into it, and all minute anatomical relations utterly obscured. The mass was dissected free, and the necessary repair made in stomach, colon and small bowel which

were implicated. The patient did very poorly after the operation and died on January 7, 1939.

The preliminary report of the surgical pathologist was to the effect that the relationship of the fistula in the specimen was impossible to describe until there was microscopic evidence for the structures involved, since it was so bound in inflammatory tissue.

The pathologist's report follows: "The specimen consists of a portion of small intestine 18 cm. in length by 3.5 cm. in circumference. The serosa is pale-gray to dark-red. The wall is edematous. The mucosa is pink-red to red in color. In addition there is a portion of transverse colon to which is attached the great omentum. At one pole the large bowel is transformed into a raised cauliflower mass 10×9 cm. in dimension. The edges of this mass are raised above the mucosa 2 cm. and are light gray to red in color. The mid portion of this mass forms a defect of 4 cm. which continues with the lumen of what appears to be the stomach near the duodenum. The mucosa here is likewise thrown up into a papillomatous mass similar to that described in the large intestine. Microscopic section of the colon reveals a mucus-producing infiltrating adenocarcinoma extending into the duodenum and stomach thus forming a *gastroduodeno-colic* fistula."

SUMMARY

1. A gastroduodeno-colic fistula is described, which presented some difficulty in the roentgen diagnosis.

2. The lesion developed from a primary carcinoma of the transverse colon.

3. The principal symptom, in common with most of the cases described by others, was sudden diarrhea after the taking of any food.

4. The perifocal inflammatory reaction obscured the anatomic relations at operation and it was necessary to mobilize the mass as such.

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MICROTIA AND CONGENITAL ATRESIA OF THE EXTERNAL AUDITORY CANAL

DEMONSTRATION OF THE EXTERNAL AUDITORY CANAL BY MEANS OF TOMOGRAPHY

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ROUTINE roentgenograms of the temporal bone do not reveal the external auditory canal clearly or consistently. Occasionally, it may be visualized in the Towne projection by using a higher kilovoltage but, at best, the outlines of the canal are indistinct because of the superimposition of the shadows of other structures. If the bone is undeveloped or sclerotic, it may be impossible to show the canal at all.

Our results in a recent study of the temporal bone by means of a simple tomograph of the type described by the late E. W. Twining[1] suggested that the method might be of value in the demonstration of the external auditory canals. Our interest was further stimulated by four recent patients who were suffering from microtia. In all four cases, the tomograms clearly revealed a complete atresia of the external auditory canal accompanying the deformity of the pinna.

The technique used is primarily designed to show the external auditory canal in two planes. Because the long axis of the canal lies in the coronal plane, a tomogram made at the appropriate level in this plane will show the canal in its entire length (*CS*, Fig. 1). A second section through a plane at right angles to this will show the canal in cross section (SS_3, Fig. 1).

TECHNIQUE

1. *Coronal Section* (*CS*, Fig. 1). The patient lies on the back with the occiput against the table and the sagittal suture in the midline. The orbitomeatal line should be perpendicular to the plane of the table top. The apparatus is then adjusted so that the plane of the section will pass through the external auditory canals, the height of which above the table top is measured directly on a scale with the patient in position. It is essential to have the head straight, because any rotation will throw

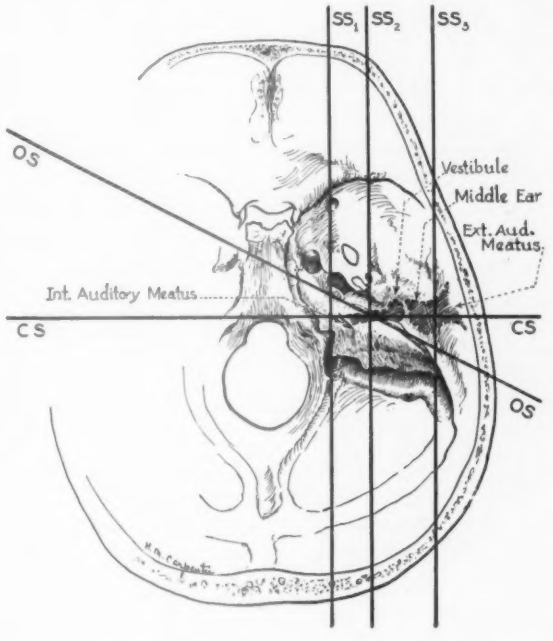

FIG. 1. Norma basalis of skull (diagrammatic) illustrating the planes of section through the temporal bone and their relation to the internal anatomy of the bone. The levels SS_3—sagittal section, and *CS*—coronal section, are used for this study.

[1] Twining, E. W. Tomography, by means of a simple attachment to the Potter-Bucky couch. *Brit. J. Radiol.*, 1937, *10*, 332–347.

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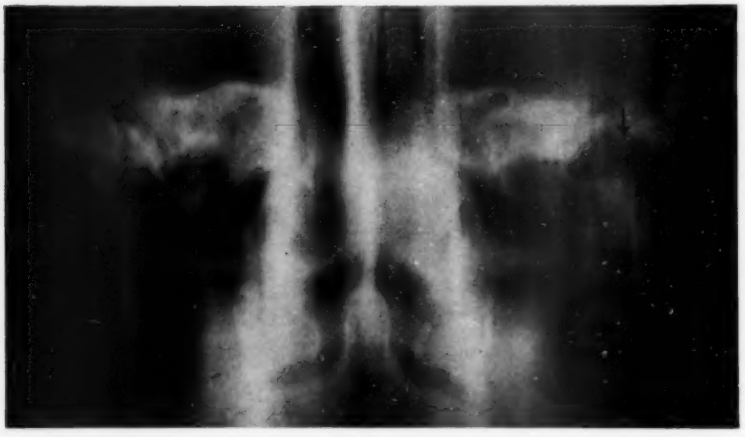

FIG. 2. Coronal plane section, revealing complete atresia of the external canal on the right side (arrows indicate the normal canal on the left). In the negative the right and left sides are reversed.

the opposite canal out of the plane of the section, and it will not be revealed for comparison. We have found an exposure of two seconds at 50 ma. using the Potter-Bucky diaphragm very satisfactory.

2. *Sagittal Section.* The patient lies prone the head being rotated until the sagittal plane is parallel with the table top, the affected ear down (this is the position for routine lateral roentgenograms). The tomograph is then adjusted to select a plane 2.5 cm. above the level of the table top (SS_3, Fig. 1). This, in the ordinary sized head, will give an image of the canal in cross section, 0.5 to 1.0 cm. lateral to the tympanum. If indicated, further films may be made at other levels. For comparison, films of the opposite side at the same levels should always be made.

COMMENT

The films obtained with this technique have all been of diagnostic quality. The coronal section film (Fig. 2) reveals the external auditory canal on the normal side in its long axis, and demonstrates the absence of a canal on the affected side. Any attempt to interpret tomograms of this region without a normal for comparison is unwise. In some films in this plane, the middle ear and the internal canal are also seen. The sagittal section (SS_3, Fig. 1) shows the normal canal in cross section (Fig. 3*a*), together with the temporomandibular joint and the mastoid process. The absence of a corresponding external canal shadow on the affected side (Fig. 3*b*) is obvious. In the interpretation of films made in this projection, there is one source of confusion. If the section has been made through the depths of the canal, close to the tympanum, the middle ear, though strictly not in the plane of focus, may be revealed as an indistinct rounded shadow (Fig. 3*b*) which may be confounded with the external canal proper, when the canal is in fact absent. On comparison with the normal side, however, it will be noted that a normal canal is irregu-

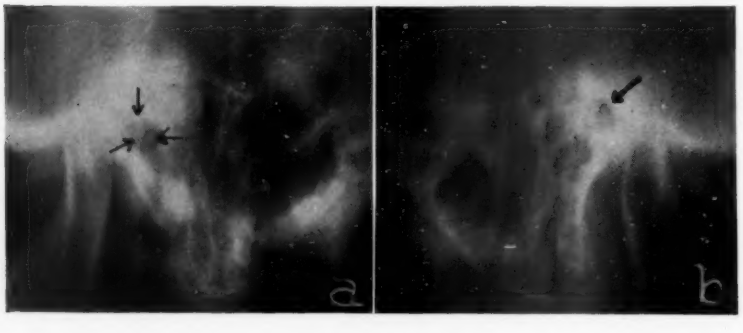

FIG. 3. Sagittal plane sections 2.5 cm. above table top: *a*, with unaffected side (left) down, revealing a normal external auditory canal in cross section (indicated by arrows); *b*, with affected side (right) down, revealing no evidence of external auditory canal. Arrow indicates shadow of tympanum.

larly ovoid in cross section rather than round, and that its boundaries are clearly defined, not blurred. If there is any doubt, a further section made more lateral will eliminate the hazy shadow of the middle ear.

There seems no good embryologic reason why microtia should not occur as an isolated defect, but the fact remains that in the majority of cases there are associated lesions, either the common atresia of the external canal or some defect in the auditory ossicles or even the labyrinth. Treatment of these patients is therefore limited as a rule to plastic operations on the deformed pinna, and it is generally agreed that surgical interference with the bone is useless owing to the frequency of concomitant defects. It is, however, possible that there are cases in which the external canal is present and in which hearing is reasonably good, and in these some form of repair might be considered. In such cases, a tomogram would be of the utmost value in giving the surgeon knowledge of the state of development of the canal. From the point of the roentgenologist, too, it is satisfying to be able to offer an anatomic diagnosis. We might remark parenthetically that we have not been able to demonstrate the ossicles by tomography, nor, on general grounds, does it appear to be feasible, at least with the simple apparatus used in this study.

No doubt the method would also be useful in the investigation of atresia due to trauma, infection, and so on, and in the demonstration of osteomas of the canal.

ROENTGENOLOGICAL AND PATHOLOGICAL CONSIDERATIONS OF EWING'S TUMOR OF BONE*

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CONSIDERABLE confusion exists regarding the clinical, roentgenological and histological criteria for the exact diagnosis of Ewing's tumor of bone. In 1922, Ewing[1] designated as a distinct type among primary bone neoplasms, a tumor arising, in his belief, from the perivascular lymphatic endothelium occurring, as a rule, in young individuals and known to be radiosensitive. Although this neoplasm is still referred to as Ewing's endothelioma of bone by some authors, many pathologists have doubted its endothelial origin. Several examples of primary bone tumor have been selected from the case record file of the University Hospital illustrating the difficulties which may be encountered in the differential diagnosis of this tumor. No attempt has been made to gather all tumors of this type from the available records. Individual cases have been selected either as typical Ewing's tumors presenting the cardinal features of this lesion or as tumors of some other type in which differentiation has been difficult.

Roentgenograms in a classical example of Ewing's tumor show the lesion located usually in the diaphysis or metaphysis of long bones. The patient is usually less than twenty-five years old, and pain, swelling, low grade fever and leukocytosis are common clinical findings. Roentgen findings in early tumor development show slight thickening and increased density of bone cortex. Later, mottled rarefaction and periosteal reaction showing lamination parallel to the long axis of bone may occur. In still later stages there may be swelling of soft parts, more bone destruction and rarely infiltration of the epiphysis. The only alteration found in the marrow cavity is irregularity and narrowing due to thickened cortex. Pathological fracture rarely occurs. The tumor is extremely radiosensitive.

Atypical variations of Ewing's tumor are often encountered. In these, roentgen examination may show only bone lysis or sclerosis. Unusual sites of origin such as spine, clavicle, skull or pelvis may be encountered. When the tumor arises in flat bones, lysis is commonly the only roentgen evidence of disease. Periosteal reaction may be absent or when present may take the form of spicule formation perpendicular to the shaft, a common sign in osteogenic sarcoma.

Necessary roentgenological differential considerations where Ewing's tumor is suspected must include any disease process which may produce any of these bone changes. There are several such lesions which must be considered. Chronic osteomyelitis and syphilitic osteitis must be ruled out and metastatic neoplasm may be confusing, particularly when found in long bones. Since tuberculosis involves the epiphyses primarily, differentiation is usually not difficult though close similarity may exist in the case of tarsal or carpal lesions. Bone involvement in leukemia is rarely solitary. In Hodgkin's disease the epiphysis is commonly involved and pathological fracture is prone to occur. Metastatic neuroblastoma and xanthomatosis must be considered, particularly in children. It is readily seen, then, that while roentgen changes may strongly suggest Ewing's tumor, confirmatory clinical and pathologic data are necessary before a definite diagnosis can be made.

The typical microscopic appearance is said to be the only constant finding in Ewing's tumor. Though this is true in some degree, the histopathology may be as variable and confusing as the roentgenogram. In the classical example, sections show dark staining round cells closely packed with practically no intercellular reticulum. The cell has

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a very thin rim of cytoplasm, a large nucleus with thin nuclear membrane and chromatin arranged in no particular pattern. In bone, masses of tumor cells invade lacunar spaces where osteoid tissue and osteoblastic activity give evidence of reactive bone formation. Osteoclasts may be found about the margins of dead bone. The tumor cells in this neoplasm do not form bone.

In atypical tumors cellular monotony is less marked and varying amounts of intercellular substance may be observed. Occasionally tumor cells show cytoplasmic processes and hyperplastic reticulo-endothelium may be present.

For an experienced pathologist differentiation between malignant neoplasm and inflammatory reaction is not difficult, and correct interpretation of the classical histologic characteristics of Ewing's tumor is easily made. However, in those tumors where histological findings are atypical, exact classification is often impossible. In many instances, without the aid of clinical knowledge it is impossible to definitely classify the neoplasm as belonging to the Ewing tumor group since the histology differs in no way from that of round cell sarcoma arising in other tissues.

Biopsy should never be omitted when Ewing's tumor is suspected. Reports to the contrary notwithstanding, there is no clinical or experimental evidence that this procedure causes dissemination of tumor cells. Incisional biopsy should be done if possible, the aspiration method being used only as a last resort.

Five tumors have been selected for presentation which are sufficiently characteristic to be considered true Ewing's tumors. The first occurred in a boy, aged fourteen, involving the proximal metaphysis of the left tibia. Roentgenograms showed both increased density and rarefaction in the cortex. Elevation of the periosteum with parallel and perpendicular bone production was present. Though infiltration extended almost to the epiphyseal line there was no invasion of the epiphysis. Since pulmonary metastasis was demonstrable at first examination, amputation was not advised and irradiation was administered to the neoplasm with good local response. This patient is alive six months after the onset of symptoms.

The next two neoplasms were located in the fibulae. The first of these developed in the diaphysis of the left fibula of a boy, aged thirteen. Roentgenograms showed cortical thickening and increased density with some distortion of the marrow cavity. There was irregular periosteal reaction without lamination, and extensive infiltration of soft tissues (Fig. 3). Death occurred four months after amputation. The other Ewing's tumor arising in the fibula showed mottled increased bone density but the predominant abnormality was lysis. Parallel deposits of subperiosteal bone as well as perpendicular spicules were present. Neither epiphysis was involved. The localized bone destruction suggested subperiosteal origin.

The next lesion (Fig. 1), although typical enough from the histopathological viewpoint, presented a very unusual roentgenological appearance. The tumor seemed to have arisen in the second cuneiform as shown by complete lysis of this bone with less extensive destruction of neighboring bones. Soft tissue swelling of the entire foot was obvious. A diagnosis of tarsal tuberculosis was made at the time of the first roentgen examination, the true identity being learned by aspiration biopsy. Following biopsy and amputation of the foot, the tumor recurred in the upper tibia and fibula and metastases were found in the lungs. Eleven months after onset of symptoms this patient died.

The next Ewing's tumor was one arising in the distal half of the clavicle. Clinically and roentgenologically this lesion was first diagnosed acute osteomyelitis. Bone rarefaction was the predominant abnormality seen in the roentgenogram though there was some cortical thickening and thin subperiosteal bone deposit. Following biopsy of the clavicle, fractionated irradiation was given with relief of pain and some roentgenological evidence of favorable response. Death occurred ten months after

FIG. 1. (379623) Ewing's tumor apparently arising in second cuneiform infiltrating surrounding soft tissue and bone.

FIG. 2. (426629) Primary malignant bone neoplasm arising in metaphysis of tibia in a male aged sixty-four in which the histology is compatible with Ewing's tumor.

FIG. 3. (412923) Ewing's tumor arising in lower fibula showing bone lysis and periosteal reaction. Appearance suggests periosteal origin.

onset of symptoms, with clinical evidence of generalized metastases.

The histopathology was so similar in these five tumors that material from one case will serve for demonstration. With low power magnification (Fig. 6) this tissue is seen to be made up of small dark cells quite closely packed with no intervening intercellular substance. More highly magnified (Fig. 7), the cells are found to be round with large dark-staining nuclei and no nucleoli. A section through bone (Fig. 8) shows invading tumor cells occupying the lacunar space, a portion of which contains osteoid tissue. Active osteoblasts are seen about the margins of the bone but there is no evidence of tumor bone formation. Other fields show islands of dead bone surrounded by osteoclasts. Reactive bone formation in response to invading tumor tissue explains the zones of increased density seen in roentgenograms. Osteoclastic absorption of dead bone accounts for the appearance of patchy bone lysis.

The next two examples represent lymphoblastoma involving bone. The first of these involving the upper portion of the left humerus occurred in a male, aged sixty-four, showing generalized lymphadenopathy. Roentgen examination disclosed a motheaten appearance of the entire upper third of the humeral shaft and pathological fracture. Mottled increased density and cortical irregularity extended into the epiphysis. There was no evidence of periosteal reaction. A roentgenogram eighteen months after irradiation showed healing of the fracture, decreased sclerosis and widening of the marrow cavity. Continued disability due to soft tissue edema prompted amputation one year later. The patient is still living six years after onset.

The other lymphoblastoma of bone (Fig. 4) occurred in a male, aged forty-five, whose first roentgenograms showed motheaten destruction in the coracoid process and neck of the scapula and also in the neighboring humeral epiphysis. There was also destruction and compression of the tenth dorsal vertebral body. Both shoulder and spine areas were irradiated with satisfactory symptomatic relief. A few months later bilateral axillary and supraclavicular lymphadenopathy developed.

Roentgen changes in both of these cases resemble those found in Ewing's tumor; however, the age of these patients, the demonstration of epiphyseal involvement

and the occurrence of pathological fracture are more characteristic of Hodgkin's disease.

Sections from the first of these, while somewhat atypical, showed a histopathologic picture compatible with Hodgkin's disease. Cells varied widely in size and shape, had abundant cytoplasm and were embedded in a rather dense bed of hyperplastic reticulo-endothelium. Sections of the soft tissues of the arm made following amputation showed extensive Hodgkin's infiltration throughout the material examined. The bone showed no evidence of tumor invasion. All of the lacunar spaces were filled with fibrous connective tissue. It is conceivable that irradiation may have completely destroyed invading tumor cells in bone—there is no reliable histopathological evidence for or against this contention.

In the second example of lymphoblastoma of bone, biopsy material was obtained from the scapula and the histopathologic classification was much more difficult. The sections showed infiltration of soft tissues and bone by a neoplasm made up of cells of various sizes and shapes with some intercellular substance. In several areas of this section the histologic appearance was compatible with that of Ewing's tumor. However, variability in cell shape and size plus the presence of reticulo-endothelium made atypical lymphoblastoma a more likely diagnosis. Undifferentiated lymphoblastoma is very similar to atypical Ewing's tumor in histopathological appearance.

The next two examples of primary bone neoplasm are shown because accurate histological classification is impossible. In the first, a boy aged nine, the body of the sixth dorsal vertebra was involved and surrounded by soft tissue infiltration. Roentgenograms showed compression deformity with narrowing of the anterior and left lateral margins of the body. There was also marked narrowing of the intervertebral space, particularly on the left. The principal bone change here was one of increased density though some rarefaction was seen in the ribs adjoining the involved vertebra.

Fig. 4. (372821) Mottled rarefaction and increased density occurring in the coracoid process of the scapula and head of humerus due to lymphoblastoma. Similar changes in tenth dorsal body with compression deformity.

The other tumor also occurred in the spine of a boy aged nine (Fig. 5). Roentgenograms showed increased density of the first lumbar body, obliteration of the intervertebral space chiefly on the right, together with kyphos deformity. There was also posterior displacement of the first lumbar body as viewed in lateral projection. Increased density and destruction of a vertebra is a very uncommon finding in a patient of this age, scarcely compatible with tuberculosis or xanthomatosis. The original roentgenological impression was metastatic neoplasm. Death occurred two

FIG. 5. (374668) Lysis and increased density in first lumbar body with narrowing of intervertebral space, and some posterior displacement caused by a tumor, the histology of which is compatible with Ewing's tumor.

years after onset of symptoms with clinical evidence of pulmonary metastasis.

In both of these tumors material for microscopic study was obtained from the tumor infiltrated soft tissues over the spine (Fig. 9). Sections show small, round, dark-staining cells infiltrating all of the tissue removed. They are quite widely spaced and show abundant intercellular substance, a portion of which is collagen from the infiltrated soft tissue. Some of the cells show cytoplasmic processes. The histopathology in both tumors, while quite atypical, is compatible with Ewing's tumor.

As pointed out by Colville and Willis[2] and Rix and Geschickter,[3] there is marked similarity in the microscopic appearance of Ewing's tumor and sympathoblastoma. The latter authors have recently reviewed all of their previously reported Ewing's tumor cases involving the spine and have found them to be sympathoblastomata. The tissues in the two tumors just described were stained with Masson's trichrome stains and Roger's silver impregnation method but failed to demonstrate any evidence of cell type compatible with sympathogonia in any of the various stages of differentiation. With the information available, these two tumors must be classified as round cell sarcomata, the general appearance of which is compatible with atypical Ewing's tumor.

There is marked variance of opinion regarding the histogenesis of Ewing's tumor. Ewing[1] originally believed the tumor rose from the perivascular lymphatic endothelium. Connor[4] points to the reticulo-endothelium as the tissue of origin. Geschickter and Copeland[5] state that the tumor is lymphocytic in origin, and Roome and Delaney[6] consider the neoplasm related to myelocytoma. There is also marked difference of opinion regarding the portion of bone in which the tumor arises. Some believe origin is within the cortex, others in the periosteum and still others believe it is within the bone marrow.

Study of the present material indicates that the tumor arises in the cortex or beneath the periosteum. In two of the neoplasms, even though they were advanced, roentgenograms showed the marrow cavity, though irregular, to be visualized throughout the entire length of the shaft. One would expect that a tumor arising in the bone marrow would produce enlargement of the cavity and thinning of the cortex, a condition which is not encountered in Ewing's tumor.

In bone sarcomas which are clinically and roentgenologically typical Ewing's tumor, the histopathology may differ widely from that usually considered characteristic. An unusual pathological picture, for example, was seen in a tumor arising in the proximal metaphysis of the tibia in a male aged sixty-four (Fig. 2). The roentgenograms showed motheaten lysis and some increased density in the upper tibia. There was a very slight degree of periosteal thickening and no evidence of subperiosteal bone production. The sections showed undifferentiated cells bearing many of the morpho-

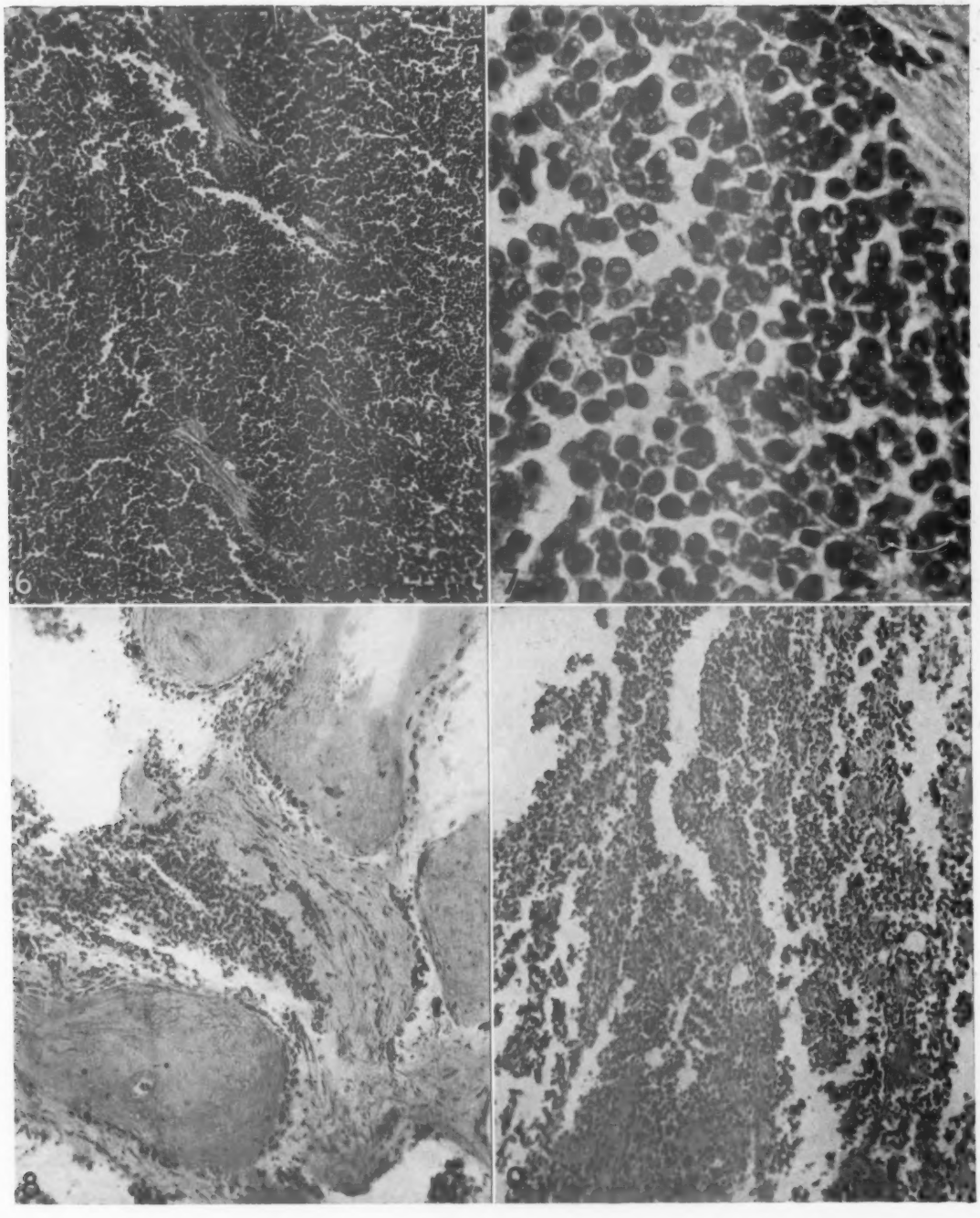

Fig. 6. (422806) Low power photomicrograph showing classical appearance of Ewing's tumor made up of small dark staining round cells with little intercellular substance.

Fig. 7. (422806) High power photomicrograph of same tumor.

Fig. 8. (422806) Appearance of same tumor in invaded bone. Lacunar space contains both tumor and osteoid tissue.

Fig. 9. (374668) Low power photomicrograph of neoplasm arising in first lumbar body. Section was taken from infiltrated soft tissue adjacent to spine.

logical characteristics of Ewing's tumor. They were uniform in size and shape but loosely arranged, many showing a tendency to spindle shape and there was abundant intercellular reticulum. The appearance of these areas was typically that of undiffer-

entiated fibrosarcoma. There were no tumor giant cells and no tumor bone formation.

There are undoubtedly some who would object to classing this neoplasm as a Ewing's tumor because of age of the patient and atypical histopathology. However, the roentgen findings are compatible with Ewing's tumor and in certain areas the histopathology is fairly typical. A tumor slightly more differentiated might conceivably form bone and would then be classed as an osteogenic sarcoma.

All of this supports the contention of Melnick[7] who maintains the cell of origin in Ewing's tumor is the undifferentiated mesenchymal cell which, in postnatal life is found about small blood vessels and capillaries. In accordance with this conception, classical Ewing's tumor is an undifferentiated round cell sarcoma composed of cells not yet differentiated sufficiently to form reticulum. In atypical neoplasms where tumor cells may be slightly more differentiated, they may assume morphologic and physiological properties of the fibroblast or fibrocyte, become spindle shaped, produce reticulum, and, with still more cellular differentiation, possibly form bone. On the other hand, differentiation may proceed along another line with production of reticulo-endothelium and myelocytic elements and may resemble the histologic picture found in lymphoblastoma. The cell of origin, then, in Ewing's tumor, fibrosarcoma, osteogenic sarcoma and lymphoblastoma is the same, histopathological classification depending on the line and extent of differentiation of tumor cells. The division of the clinical entities becomes arbitrary and must be based on clinical, roentgenological and histopathological criteria.

If, as is suggested, Ewing's tumor is an extremely undifferentiated round cell sarcoma of bone the question arises—is such a separate classification justified? It would seem that this clinical grouping is justifiable and serviceable provided it is understood that this designation does not imply a separate neoplastic entity. Therefore, Ewing's tumor constitutes an intergradation with lymphoblastoma and myeloblastic tumors, on the one hand, and with fibrosarcoma and osteogenic sarcoma, on the other.

CONCLUSIONS

1. Ewing's tumor represents an arbitrary subdivision of malignant bone neoplasms. Histopathologically it cannot be considered a neoplastic entity.

2. Roentgen signs of Ewing's tumor are not unequivocally characteristic. They result from destructive and reparative processes in osseous tissue any of which may be seen in osteogenic sarcoma, metastatic tumor or non-neoplastic lesions.

3. Correlation of clinical, roentgenological and histopathological data is necessary in order to establish the correct diagnosis and proper classification of primary bone tumors.

4. Biopsy should be done as early as possible in any bone lesion where primary neoplasm is suspected.

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QUIESCENT INTERVAL AND BONE METASTASES IN LYMPHOSARCOMA*

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BOTH the duration of the quiescent interval and the frequency of occurrence of bone metastases seem significant factors in the prognosis of lymphosarcoma. Little attention seems to have been paid to either of these factors, however, except in special instances. The fact that the case here reported presented unusual features in both these respects has been responsible for a review of these aspects of lymphosarcoma.

LITERATURE

Regarding duration of the quiescent interval, Craver's[1] data in 96 cases show a total number of 7 cases (7 per cent) surviving for more than five years. The average survival since admission in this group of 7 cases is 7.3 years. Of Cutler's[3] 16 cases in which death occurred, only 1 survived more than four years. Of the living patients in his series 4 out of 13 were alive after four years, while 2 others were alive after more than 5.5 years. Minot and Isaacs[5] reported 1 patient well after six years.

Bone metastases in lymphosarcoma have received very little attention. As noted by Craver and Copeland[2] few if any reports of large series of cases provide information on this aspect of lymphosarcoma. In Craver and Copeland's series of 164 cases, 17 (10 per cent) had bone involvement. In cases with bone involvement the following characteristics were apparent. Metastases were noted from twenty days to one year prior to death. Most patients died before the end of the third year. Bone involvement in order of frequency was spine, pelvis, skull, femur, humerus, tibia, scapula, mandible, fibula, and ribs. Lesions in the bones were either osteoplastic or osteolytic, with the latter predominating. *All the metastases originated from reticulum cell sarcomas.*

REPORT OF CASE

T. E. D., a male, white, aged forty-eight, first noted the onset of generalized enlargement of the lymph nodes in August, 1932. Subsequently there was a slow, progressive increase in size so that in April, 1933, he consulted a physician. Upon examination at that time by Dr. H. D. Meeker, there were "numerous discrete nodules in each submaxillary space and in both carotid chains. There were small but palpable glands in both axillae and both groins." There was no elevation of temperature, no chest nor abdominal symptoms and a roentgenogram of the chest showed no enlargement of the mediastinal lymph nodes. On April 21, 1933, hemoglobin was 105 per cent, erythrocytes 5,600,000, and leukocytes 5,400. A differential count of the leukocytes showed 75 per cent polymorphonuclears, 24 per cent lymphocytes and 1 per cent eosinophiles.

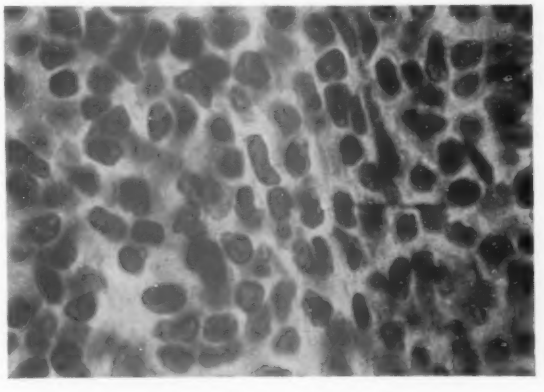

Fig. 1. Biopsy specimen inguinal lymph node, May 9, 1933.

Biopsy of two inguinal lymph nodes on May 9, 1933 (slides and reports furnished by Drs. H. D. Meeker and H. R. Muller) showed (Fig. 1) an overgrowth of small round cells such that the normal architecture of the lymph node was partially destroyed. No eosinophiles nor Dorothy Reed cells were present.

Following roentgen treatment and a vacation

* Read at the meeting of the American Association for the Study of Neoplastic Diseases, Washington, D. C., Sept. 10, 1937.

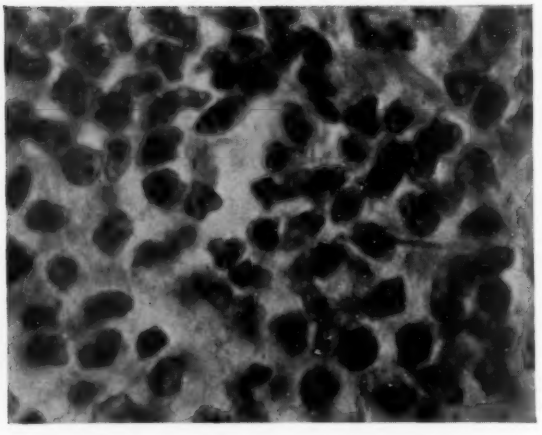

FIG. 2. Histological appearance of popliteal lymph node removed at biopsy April 12, 1937.

of six months in Florida, the patient remained well until December, 1936. At that time he was seen because of pain in the right chest. Following an evening of group singing he noticed a gradually increasing discomfort in the right chest, which discomfort at times felt like "gas pushing upwards" on the right side. He was unable to take a deep breath. Physical examination revealed a very slight icteric tinge to the skin, pale mucous membranes, and generalized glandular enlargements. All superficial lymph nodes were enlarged, particularly the axillary and left popliteal, these being approximately 2 cm. in diameter. Roentgenoscopic examination of the chest, together with roentgenograms, showed a marked widening of the mediastinal shadow, a thickened interlobar pleura and a slight increase in density in the lateral portion of the right lung in the region of the third, fourth and fifth ribs. Following a series of roentgen treatments the patient by January 22, 1937, reported that he was feeling well, breathing much better and that he could breathe without difficulty.

A second series of roentgenograms taken on February 9, 1937, showed a return to normal size of the mediastinal lymph nodes, disappearance of the interlobar thickening, but a persistence of the shadow in the lung.

Beginning on March 27, 1937, the patient experienced an upper respiratory infection which gradually increased in severity such that his temperature for several days reached 103° to 104° F. Cough was considerable and was accompanied by recurrence of pain in the right chest. This pain having increased, on April 12, 1937, the third series of roentgenograms was taken. Corresponding to a palpable mass 3 by 5 cm. was the area of increased density and the fracture of the rib. Physical examination at this time revealed barely palpable axillary and inguinal lymph nodes, non-palpable cervical, posterior-occipital and epitrochlear lymph nodes and the left popliteal lymph node 2 cm. in diameter. Temperature ranged around 99.2° F. A mass 15 by 20 cm. was palpable in the abdomen, near the umbilicus.

On April 12, 1937, biopsy of the left popliteal lymph node, which had received no roentgen treatment, was done. Histologically the tissue was composed entirely of small lymphocytes, some of which were seen in mitosis. There was some fibrosis but neither eosinophiles nor Dorothy Reed cells were present (Fig. 2). These findings were essentially the same as those of Meeker and Muller four years previously.

Following this, the patient received large doses of roentgen therapy to the abdominal mass. Even on May 27, 1937, he weighed 157 pounds, a loss of only 8 pounds from his maximal weight. The cough continued with slight remissions, fluid collected in the abdomen and he died on June 25. Autopsy was not obtained.

DISCUSSION

The present case is interesting from several standpoints. First is the relationship between histological appearance and the quiescent interval. The patient went for a period of four years without sufficient symptoms to necessitate consulting a physician or communicating with his physician who previously had made a definite diagnosis of lymphosarcoma from the biopsy.

In the literature, the "simple lymphomata," "lymphadenomata" or "hyperplastic lymphadenitis" cases are associated with long clinical courses. Le Count's[4] case of this type continued for fifteen years, while one of Ewing's cases (Cutler[3]) continued for eighteen years, with fatal outcome. In none of these cases was there metastasis to bones while conversely in none of Craver and Copeland's cases with bone metastasis was the lymphosarcoma of the type reported. The histological appearance of the lymph nodes in the case

here reported, similar at both beginning and end of the disease, is that of a supposedly benign lymphatic tumor. *Its metastasis to bone, previously reported as occurring only in the reticulum cell type of lymphoma, therefore is very unusual.*

The metastic lesion in the rib was predominantly osteolytic in type. In one of Craver and Copeland's cases (their Case 5) "a lesion in a rib showed rarefaction without marked alteration in the structure of the bone," apparently without pathologic fracture.

As in most cases of bone involvement, attention was called to the rib metastasis by pain locally. It seems unusual that the rib metastasis became evident soon after such excellent response to roentgen treatment had been obtained upon the part of the mediastinal lymph nodes.

According to the frequency of occurrence, metastases of lymphosarcoma to ribs are very rare. Craver and Copeland, however, do state that bone involvement, particularly of the vertebrae, occurs chiefly through extension, and it is probable that the rib in the case here reported was involved in that fashion.

SUMMARY

A case of lymphosarcoma of round cell type with four years' quiescent period and metastasis to bone (rib) is reported.

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INTRACRANIAL COMPLICATIONS FOLLOWING IRRADIATION FOR CARCINOMA OF THE SCALP*

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WE have observed fatal intracranial complications in 3 patients who received large doses of radiation for carcinoma of the scalp. The purpose of this communication is to call attention to the therapeutic procedures employed in these patients and to record their operative and post-mortem findings.

FIG. 1. Case 1. Note denuded bone in center of lesion at *A*. Photograph taken in February, 1937.

CASE 1. O. McH., male, aged sixty, was admitted February 10, 1937, complaining of an ulcer of the scalp of eleven years' duration (Fig. 1). The lesion was first treated with radiation five years prior to his present admission. The quality and quantity of radiation employed were unknown though we believe low voltage rays were employed as the treatment was given by a dermatologist. In November, 1935, the patient was again irradiated. During the following twelve months, the lesion was treated at various intervals with high voltage radiation (200 kv., 50 cm. skin-target distance), receiving a total of 5,000 r filtered through 0.50–0.75 mm. of copper (Fig. 2).

The patient was first seen in the Department of Radiology of the Hospital of the University of Pennsylvania on February 10, 1937. On ex-

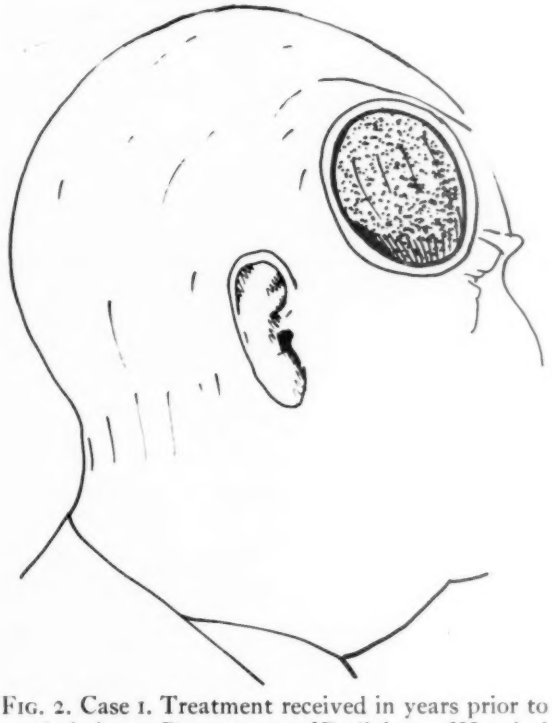

FIG. 2. Case 1. Treatment received in years prior to admission to Department of Radiology of Hospital of University of Pennsylvania, February, 1937. Before November, 1935: Superficial therapy, total dose and physical factors unknown.

November, 1935—November, 1937

November, 1935 —1,000 r in 5 days (0.5 mm. Cu)
March, 1936—1,600 r in 4 days (0.5 mm. Cu)
September, 1936—2,000 r in 16 days (0.75 mm. Cu)
November, 1937—1,000 r in 7 days (0.75 mm. Cu)
Physical factors, 200 kv., 50 cm. skin-target distance.

* From the Departments of Radiology and Neurosurgery of the Hospital of the University of Pennsylvania, Philadelphia. Read at the Thirty-Ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 20–23, 1938.

amination, a foul, necrotic, sloughing ulcer (Fig. 1), 13 cm. in diameter, was found overlying the right frontal bone. The bone in the center of the involved area was denuded. The edges were raised with considerable infiltration evident in the outer canthus and upper lid of the right eye. No metastatic nodes were palpable in the cervical region.

Biopsy showed spinocellular carcinoma, Grade 2.

Laboratory Data. Blood chemistry and serology, negative.

Roentgen Examination. There was a demineralized area in the frontal bone on the right side due either to infection, malignant disease, or both.

Therapeutic Course. The patient received his first roentgen treatment from us on February 10, 1937. The entire lesion was divided into six fields, each 7 cm. in diameter (Fig. 3). One portal was treated daily, 350 r* being delivered at each sitting. The rays were emitted by an oil-cooled, air-insulated, shock-proof tube energized by a 200 kv. constant potential generator operating at 15 ma. (ripple 3 per cent). The target skin distance was 18 cm. A Thoraeus filter equivalent to 5 mm. of copper (1.25 mm. tin, 0.25 mm. Cu, 1.0 mm. Al) was employed, the afflux being 160 r a minute. The patient received 2,000 r to each of the six portals in fifty-five days which produced a moderately severe epithelitis exudativa. On April 12, 1937, two weeks after the last treatment, a biopsy revealed evidence of active malignancy. Following a consultation with another radiologist, the lesion was given an additional 2,000 r to each of two portals in six days (Fig. 4). Examination in June, 1937, revealed considerable slough in the center of the ulcer with continued healing about its periphery.

Several days later, June 17, 1937, the patient complained of loss of control of the fingers of

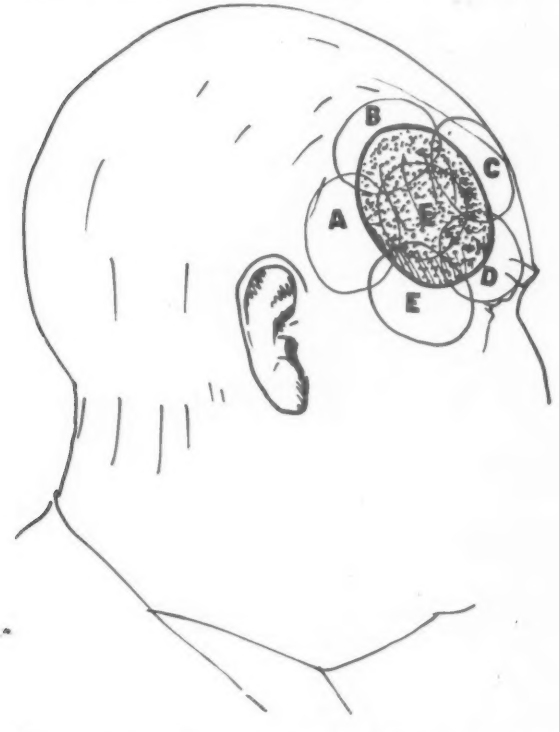

Fig. 3. Case 1. Treatment received February, 1937–March, 1937. Portals *A*, *B*, *C*, *D*, *E*, *F*, 7 cm. diameter, daily dose, 350 r to one area; total dose, 2,000 r×6; total treatment period, fifty-five days. Physical factors: oil-cooled air-insulated shock-proof tube, constant potential generator, 200 kv. (peak), 15 ma. 3 per cent ripple, 18 cm. skin-target distance; 5 mm. Cu equivalent filtration (Thoraeus, 1.25 mm. tin, 0.25 mm. Cu, 1.0 mm. Al); 160 r per minute delivered to skin with these factors.

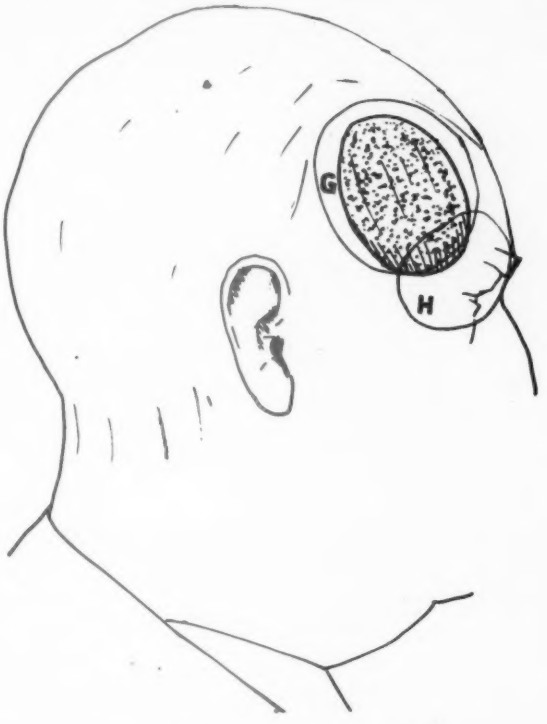

Fig. 4. Case 1. Treatment received April, 1937–May, 1937. Portal *G*, 9 cm. diameter; daily dose, 400 r; total dose, 2,000 r; total treatment period, six days. Portal *H*, 7 cm. diameter; daily dose, 400 r; total dose, 2,000 r; total treatment period, six days. Physical factors: Same as in Figure 3.

* r = in air without back-scatter.

his left hand. He was drowsy and complained of headache. A roentgen examination of the skull revealed no pineal shift. The bone demineralization previously reported had progressed though it was impossible to tell from the roentgenograms alone whether the bone changes were due to infection, malignancy, or both. Because of these findings, the patient was hospitalized.

Following operation, the patient's headache subsided and the weakness of the arm and leg disappeared. A culture of the material obtained from the cavity in the brain showed both *Staphylococcus albus*, and *Streptococcus haemolyticus*.

Seven days after operation, the original clinical picture began to return, the patient developing left hemiparesis and stupor. The

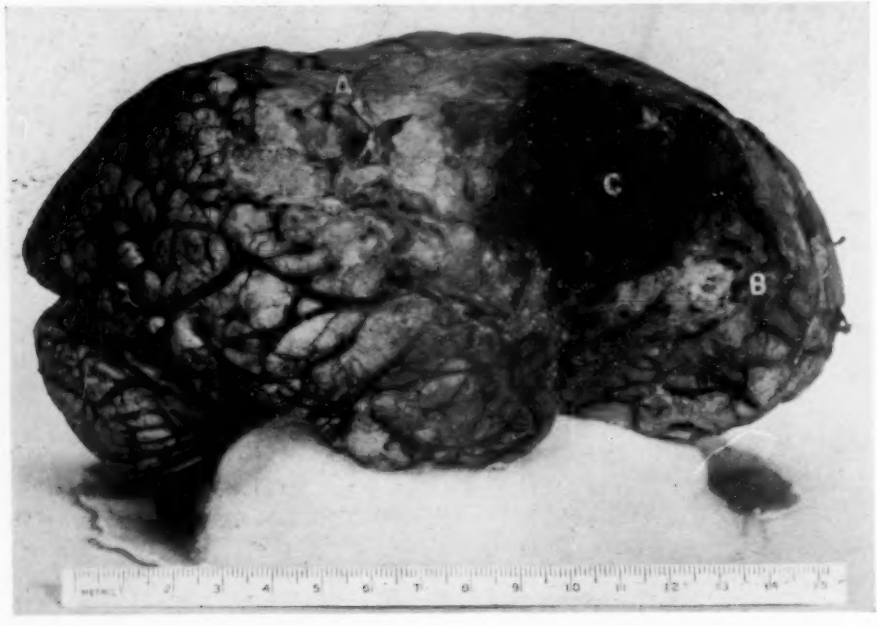

FIG. 5. Case 1. Right lateral view of brain showing the diffuse inflammatory reaction more marked at *A* and *B*. Area *C* is the site of the primary focus of infection where brain herniated into cranial defect.

Physical and Neurological Examination. Upon admission to the hospital, the patient's temperature was 102° F., pulse 80 and respirations 24. The blood pressure was 124/68. The edges of the ulcerated area of the scalp were inflamed and reddened. The right eyelid was edematous. The cranial nerves were essentially negative. The eyegrounds showed haziness of the disc margins. The left arm and leg were weaker than the right and their reflexes were increased.

On June 17, 1937, a trephine was made through the exposed bone over the lower portion of the motor area. The dura was white, thickened and did not pulsate. After opening the dura, a beefy-red arachnoid was exposed. Upon inspection and manipulation, a large cavity was opened which contained yellow fluid with "strings" of exudate. A rubber tissue drain was inserted and dressings applied.

trephine was enlarged at a second operation by rongeur. *The bone removed was dry and thin. It did not have the appearance of osteomyelitis.* A foul-smelling, greenish exudate was present over the entire brain exposed. Degenerated brain substance was removed and adequate drainage obtained. The patient's condition was not altered. Two days after the second operation, the patient died.

Pathological Examination. At autopsy the brain, upon gross inspection, was covered by an extremely thick, milky, suppurative exudate (Fig. 5). The base of the brain and brain stem were likewise covered by this intense suppuration (Fig. 6). The ependymal lining of the lateral ventricles was covered by a thick white exudate. This was particularly heavy on the roofs of the anterior horns of the ventricles, attaining a thickness of almost 0.5 cm. This

thickening of the ependyma and suppurative exudate were also present in the third and fourth ventricles.

The vessels of the brain showed marked congestion and numerous hemorrhages were present throughout. The right half of the dura was thickened and revealed an internal suppurative process. A diagnosis of suppurative meningitis extending over the entire brain was made together with a thickening of and suppurative exudate over the entire ependyma of the lateral ventricles.

Microscopic Description (Dr. B. J. Alpers). "There is a very thick exudate covering the cortex. The lower layers next to the cortex are composed of a dense fibrous exudate in which there are many lymphocytes and an occasional large mononuclear cell. The more superficial parts of the exudate are composed of polymorphonuclear leukocytes which lie in scattered strands of fibrin. The pial vessels are thickened and their walls infiltrated by leukocytes. The cortical vessels show swelling and proliferation of the endothelium. There is extensive infiltration of the brain tissue with leukocytes. Fresh hemorrhages are seen here and there. The ganglion cells are swollen. Collections of leukocytes are present everywhere in the brain tissue. *Diagnosis:* Meningo-encephalitis—purulent."

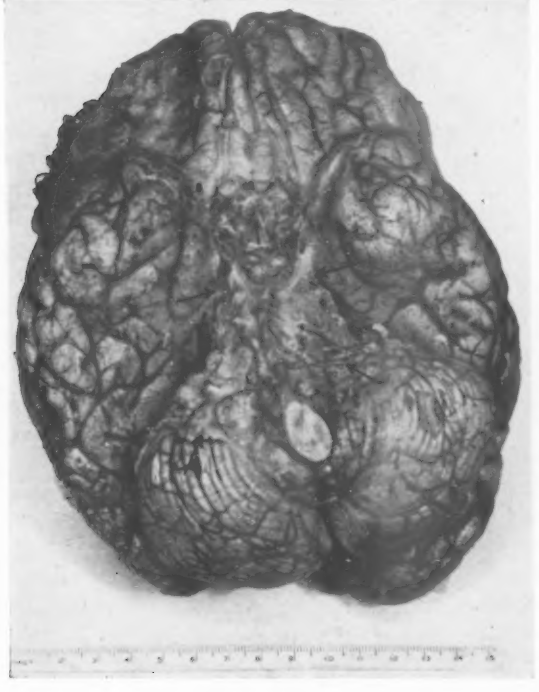

Fig. 6. Case 1. Base view of brain showing the marked basilar meningitis.

Fig. 7. Case 11. Note the denuded bone (arrow). Photograph taken in March, 1937.

Summary of Case 1. The patient, aged sixty, received an unknown amount of low voltage rays for a cancer of the scalp five years prior to his present admission. High voltage radiation, 200 kv., was then directed to the lesion at irregular intervals for twelve months before the patient was first seen by us, the lesion receiving 5,000 r during this period. Two months later, the lesion received 2,000 r × 6 in fifty-five days of high voltage radiation in our department. The patient was given an additional 2,000 r to each of two portals three weeks later for evidence of residual malignancy. The patient developed evidence of an intracranial lesion six weeks after the last treatment. A dural and subdural infection was found and drained. The patient ultimately succumbed to the intracranial infection and died. A diffuse purulent meningo-encephalitis was found at autopsy.

Case 11. H. B., male, aged fifty-three, was admitted March 27, 1937, complaining of an ulcer of the scalp of nine months' duration. During this time the lesion had been treated

with caustic salves applied locally without success. On examination, an ulceration in the scalp, 10 cm. in diameter, overlying the left parietal bone was found (Fig. 7). The edges were indurated and the entire area exuded pus. Several enlarged nodes in the posterior cervical chain suggested metastasis.

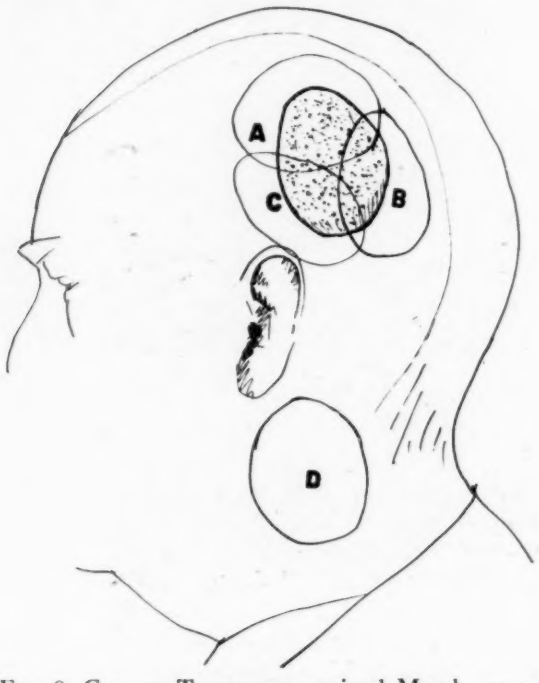

FIG. 8. Case 11. Treatment received March, 1937–April, 1937. Portals *A*, *B*, *C*, 9 cm. diameter; daily dose, 400 r to one area; total dose, 2,100 r×3; total treatment period, sixteen days. Portal *D*, 9 cm. diameter; daily dose, 300 r (every other day); total dose, 2,800 r; total treatment period, fifteen days. Physical factors for portals *A* and *B:* Same as in Figure 3.

Biopsy showed squamous cell carcinoma, Grade 2.

Laboratory Data. Blood chemistry and serology, negative.

Roentgen Examination. The bones of the vault were negative.

Therapeutic Course. Treatment was started on March 30, 1937. The entire lesion was divided into three fields, each 9 cm. in diameter (Fig. 8). Another 9 cm. circular portal was directed into the metastatic cervical nodes. The lesion in the scalp was treated daily, 400 r being delivered through one portal per day. In addition, the metastatic nodes received 300 r at each sitting. The rays were emitted by an oil-cooled, air-insulated, shock-proof tube activated by a 200 kv. constant potential generator operating at 15 ma. The target-skin distance was 18 cm. A Thoraeus filter equivalent to 5 mm. of copper (1.25 mm. tin, 0.25 mm. Cu, 1.0 mm. Al) was employed, the intensity being 160 r per minute. The patient received 2,100 r to each of the three portals over the skull in sixteen days. The metastatic nodes in the neck received 2,800 r in fifteen days.

The lesion in the skull developed a moderately severe epithelitis exudativa which began to heal in two weeks. The metastatic nodes became smaller and freely movable. On June 5, 1937, because of the marked improvement in the scalp lesion, burr holes were drilled into the denuded bone to hasten granulation tissue formation. *At operation, the soft texture of the bone was noted.* The metastatic nodes were surgically removed. Subsequently, these nodes proved to be invaded by squamous cell carcinoma.

On June 11, 1937, the patient began to have difficulty talking. Words were not pronounced correctly. This increased until the time of admission, when his speech was limited to one or two words. At about the same time, the right hand became clumsy, with some loss of motor power. The day before admission, the patient had a jacksonian convulsion on the right, becoming generalized before completion.

Physical and Neurological Examination. On admission, June 15, 1937, the patient was stuporous. The right arm was weak and there was a reduction of sensation over the right arm, right shoulder, and the right side of the neck. The patient had an aphasia which was almost complete. The eyegrounds showed early choking.

On June 15, 1937, a left occipitoparietal craniotomy was performed. Upon opening the dura, pus exuded from between the dura and brain. The location of the abscess was directly beneath the upper portion of the ulcerated scalp. Appropriate drainage was instituted. The pus culture revealed staphylococci.

Convalescence was slow. One week later, an exploration for a subcortical abscess was made but none found. Following this the power and stereognostic sense returned in the right arm and the aphasia cleared completely. The patient was discharged from the hospital on June 24, 1937.

The patient was readmitted July 7, 1937, because of hemorrhage which had occurred from

under the ulcerated scalp edge. Examination did not reveal the source of hemorrhage and after two days' observation, the patient was discharged.

Five days after discharge, the aphasia and weakness of the right hand and arm returned. On July 10, he was readmitted to the hospital. Two days later, the bone flap was removed together with some cerebral tissue beneath the cranial defect. This tissue, on histological examination, proved to contain evidences of a process extended into the substance of the brain for a distance of 3 cm. In the right anterior portion of the first temporal convolution, 1 cm. below the surface of the cortex, there was a round, apparently encapsulated tumor mass measuring 1 cm. in diameter (Fig. 10).

Microscopic Description of Brain (Dr. B. J. Alpers). "There are two types of tissue reaction: (1) a vascular process, and (2) a tumor.

Vascular process: In the right hemisphere beneath the ulcerated scalp lesion is a definite

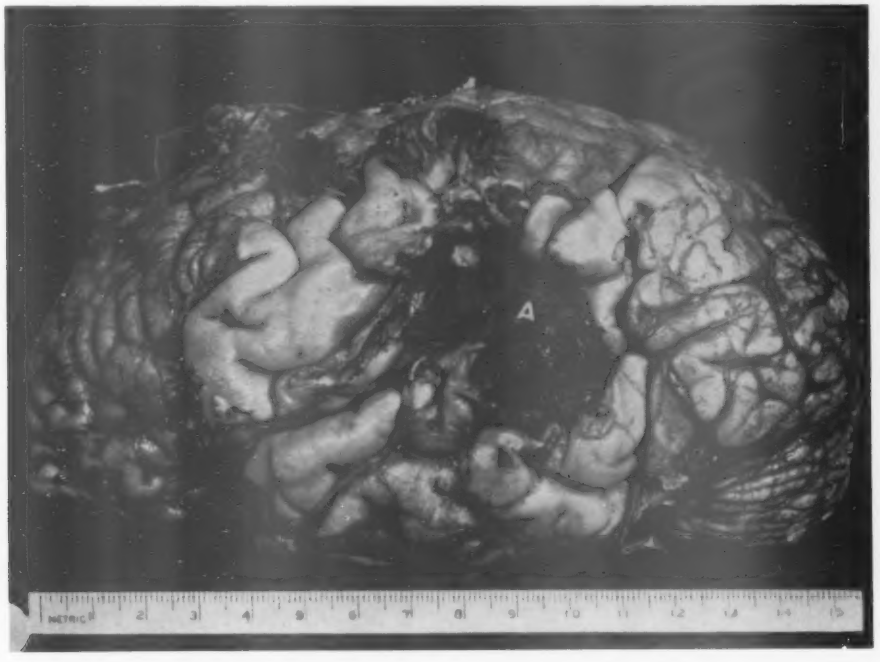

Fig. 9. Case 11. Left lateral view of brain. *A* shows the degenerated and softened area, the result of vascular occlusion. This area occurred directly beneath the scalp lesion.

low grade infection and fresh hemorrhage. Following the removal of the bone flap, a cerebral fungus—herniation—developed and in this state, the patient continued until August 22, when he developed bronchopneumonia and died.

Gross Description of Brain. Except for a hard hemorrhagic area beneath the cranial defect on the left side in the region of the angular gyrus and widening of the surrounding gyri, there was nothing of note to be seen on gross inspection of the brain (Fig. 9).

Coronal sections of the brain were made after it had hardened properly (Fig. 10). A section through the hard hemorrhagic area in the region of the left angular gyrus disclosed that the pathological process. This is characterized by changes in the vessels and in the surrounding brain tissue. The middle cerebral artery shows almost a complete obliteration of its lumen due to internal proliferation. There has been canalization of this process. The proliferated tissue is fibroblastic. There is no evidence of inflammation within it. The elastica is broken in many pieces. There is no adventitial reaction either inflammatory or otherwise. A few of the other vessels show beginning internal changes. The brain tissue shows softening, with numerous gitter cells. There is also much fibrosis and gliosis in the tissue with formation of a capsule. Vessel proliferation is also seen. Areas of glial proliferation are numerous. These are chiefly

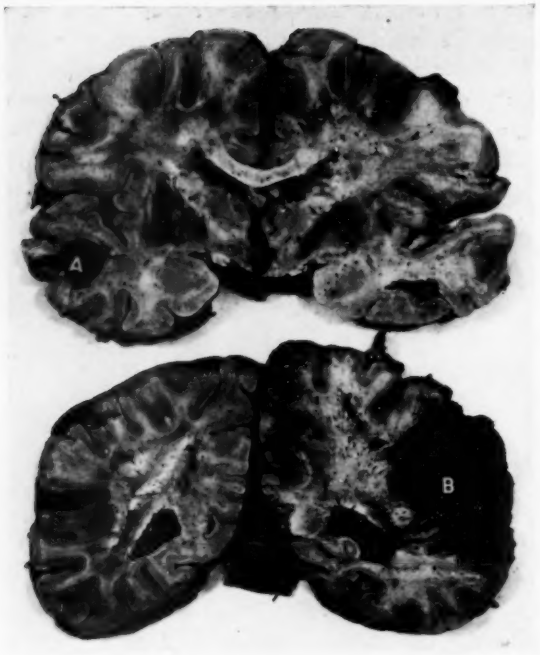

FIG. 10. Case II. Coronal sections of brain. The metastatic nodule is shown at *A*. The degenerated area is seen at *B*.

astrocytes. Lymphocytes and plasma cells are found in large numbers in these areas. Vessel proliferation is found in large numbers. *Diagnosis:* (1) metastatic carcinoma; (2) endarteritis; (3) old softening.

"Tumor: In the left temporal lobe, there is a tumor nodule which is clearly defined but which has no capsule. It extends into the brain tissue slightly. It is composed of large numbers of cells. These have a round, large, roomy cytoplasm which takes a pale acid stain which is frequently filled with vacuoles. The nucleus shows a marked degree of metamorphosis. Its shape varies so widely as to be indescribable. It has all sorts of shapes; it is often multiple, with cytoplasmic bridges connecting the various parts. It is heavily chromaticized and contains many vacuoles of varying sizes and numbers. Amitotic division is frequently seen. Mitoses are seen occasionally. There are many large sinuses within the tumor but very little connective tissue. The surrounding brain tissue shows very little."

Summary of Case II. The patient, a male, aged fifty-three, received 2,100 r to each of three areas directed into a squamous cell carcinoma of the scalp in sixteen days. Several metastatic cervical nodes were also treated. The nodes were subsequently excised and contained carcinoma. The lesion regressed rapidly. Burr holes were drilled into the calvarium to hasten granulation tissue proliferation. Eight weeks after the last treatment, signs of an intracranial infection developed. A subdural abscess was drained but the patient died. At autopsy, a large abscess was found in the brain. Even more unusual, was a sizable metastatic nodule in the contralateral temporal lobe. The metastatic foci in the cervical nodes and brain merit special comment as we have never observed similar metastases in patients with carcinoma of the scalp.

CASE III. T. B., male, aged forty-seven, was admitted April 12, 1930, complaining of an ulcer of the scalp of nine years' duration. During these years, the lesion had been treated with bland ointments, caustics, desiccants, and roentgen rays without success.

FIG. 11. Case III. Photograph taken February, 1932, before the lesion was desiccated.

On examination, an annular lesion, 4 cm. in diameter, was found overlying the parieto-occipital region (Fig. 11). The bone was not exposed.

Biopsy showed a basal cell carcinoma.

Laboratory Data. Blood chemistry and serology, negative.

Therapeutic Course. On April 12, 1930, the lesion was treated by means of ten radium tubes filtered through 0.3 mm. of alloy metal. The total amount of radium contained in these tubes was 150 mg., the lesion being given 270 mg-hr. of radium in one hour forty-eight minutes (contact). The area healed completely in seven weeks. One year later, April 17, 1931, three recurrent nodules were noted in the margin of the scar. The area was again treated by means of three 100 mg. radium tubes contained in applicators with a wall thickness of 2 mm. of brass placed in contact with the skin, the lesion receiving 150 mg-hr.×3 in one and a half hours. On June 16, 1931, the area was again treated by means of radium for recurrence. Two 50 mg. and four 100 mg. radium cells filtered through 0.3 mm. of alloy metal were employed in contact with the skin. The 50 mg. applicators were applied for thirty-five minutes and the 100 mg. applicators for seventy minutes, delivering a dose of 29 mg-hr.×2 and 115 mg-hr.×4, respectively. On September 30 and October 1, 1931, the carcinoma was again treated. Thirteen radium tubes each containing 50 mg. of radium filtered through 2 mm. of brass were employed at a distance of 0.5 cm. Nine portals were treated, each receiving a total of 200 mg-hr. of radium. The reaction was severe but the lesion failed to disappear completely. On February 11, 1932, the bone was denuded with an endotherm knife (Fig. 13). Healing was rapid and complete. Several months later, the denuded bone was spotted with burr holes to promote granulation tissue proliferation. Roentgen examination of the skull in March, 1933, revealed a localized area of bone destruction in the region of the burr holes. The rarefied area was well circumscribed. The inner table of the skull was intact.

In July, 1933, biopsy from a suspicious margin of the lesion revealed basal cell carcinoma. The patient then received 5,000 r of unfiltered radiation and 2,600 r filtered through 0.25 mm. Cu in four days, July 21 to 24, 1933. The rays employed were emitted by an air-cooled, mechanically rectified unit operating at 135 kv., 5 ma. The target skin distance was 30 cm., field 9 cm. in diameter, afflux being 100 r a minute for unfiltered radiation and 25 r a minute for 0.25 mm. Cu plus 1 mm. Al. In November, 1933, another biopsy proved positive and an additional 7,000 r of unfiltered radiation and 1,200 r with 1 mm. Al were delivered to the lesion on December 4 to 5, 1933. Roentgen examination of the head at this time revealed no change in the characteristics of the bone defect since the examination in March, 1933.

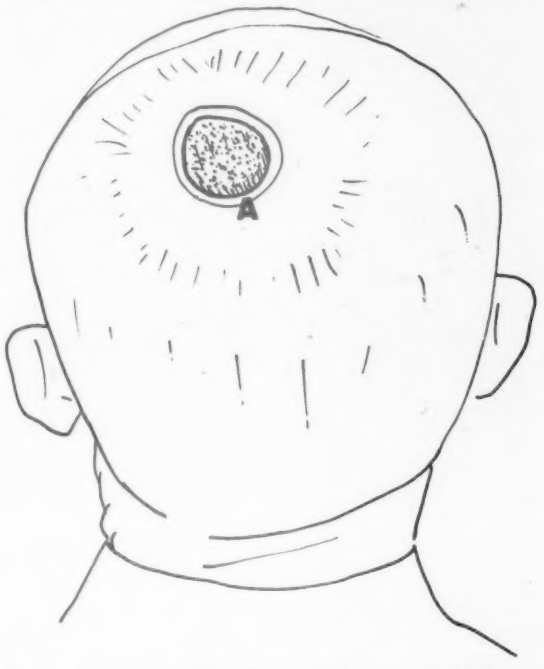

Fig. 12. Case III. Treatment prior to admission to Department of Radiology, April, 1930, ointments, desiccants, caustics, irradiation. Treatment received in our department April, 1930–April, 1933:

Portal *A*

April, 1930—27 mg-hr.×10 radium (0.3 mm. alloy, contact, 1 hr. 45 min.)
April, 1931—150 mg-hr.×3 radium (2 mm. brass, contact, 1 hr. 30 min.)
June, 1931—29 mg-hr.×2 radium and 115 mg-hr.×4 radium (0.3 mm. alloy, contact, 35 min.)
September, 1931—200 mg-hr.×9 radium (2 mm. brass, 0.5 cm. distance, 5 hr. 10 min.)
February, 1932—electrothermic resection.
March, 1933—burr holes drilled into calvarium.

In February, 1934, the denuded bone began to suppurate. A foul-smelling osteomyelitis rapidly developed which was treated with maggots in April, 1934. In May, 1934, the patient began to develop signs of an intracranial

FIG. 13. Case III. Photograph taken February, 1932, after electrothermic removal of the basal cell carcinoma. Note the denuded bone at *A*.

lesion. An extradural abscess was exposed and drained. The bone continued to sequestrate. In June, 1934, the bone was completely destroyed allowing the dura to bulge into the wound and break down.

The dura eventually degenerated, the brain lying exposed in the infected ulcer bed. The patient died shortly thereafter of a diffuse streptococcic meningitis. A post-mortem examination was not permitted.

Summary of Case III. The patient, a male, aged forty-seven, received 2,750 mg-hr. of radium in eighteen months to a basal cell carcinoma of the scalp (Fig. 12). Later, a recurrence was removed surgically leaving denuded bone. The bone was subsequently spotted with burr holes to promote granulation tissue proliferation. Another recurrence developed which received 15,200 r of low voltage radiation in five months (Fig. 14). Osteomyelitis of the calvarium developed which progressed until a large portion of the dura became exposed. The dura and brain subsequently degenerated. A diffuse streptococcic meningitis caused death. Autopsy was not obtained.

COMMENT

The intracranial symptoms which developed in the patients being reported were those of increased intracranial pressure—namely, choked discs, stupor, and headache. The focal signs and symptoms were referable to the portion of the brain beneath the scalp lesion. Case I died of a purulent meningo-encephalitis. Case III died of a streptococcic meningitis. Both patients received large quantities of radiation over a period of years. Case II was given the smallest amount of radiation. Death in this patient was due to an obliterative endarteritis and brain softening. In each

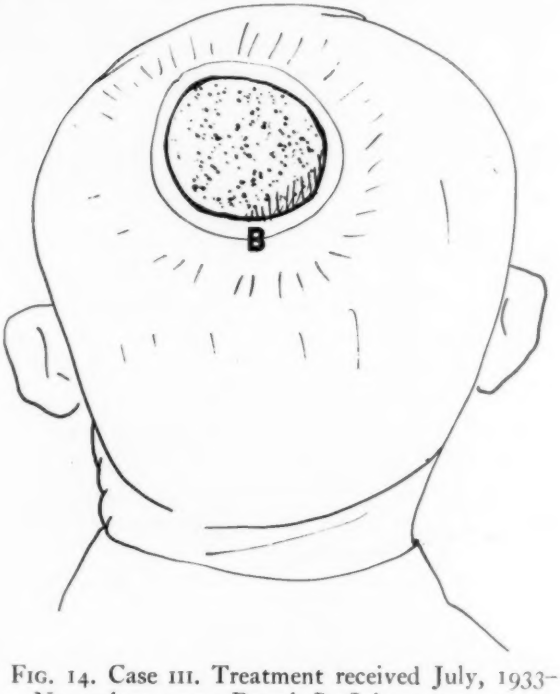

FIG. 14. Case III. Treatment received July, 1933–November, 1933: Portal *B:* July, 1933, 5,000 r in four days (unfiltered); 2,600 r in four days (0.25 mm. Cu); November, 1933, 7,000 r in two days (unfiltered); 1,200 r in two days (1.0 mm. Al). Physical factors: air-cooled nonshock-proof tube, mechanical rectifier; 130 kv., 5 ma., 30 cm. skin-target distance; 100 r per minute delivered to skin with these factors, unfiltered; 25 r per minute delivered to skin with these factors (0.25 mm. Cu plus 1 mm. Al).

instance, the first craniectomy revealed a focal subdural abscess. In Case I and Case II the abscess developed at six and eight week intervals following irradiation. The abscess in Case III developed six months after irradiation.

Extensive carcinomas of the scalp are frequently associated with bone changes attributable to infection, malignant disease, or a combination of both. It is often impossible to distinguish between these destructive processes. Under such circumstances, the clinical findings are of paramount significance. When infected, the cranium losses its shiny, glistening appearance, becoming dull, gray or grayish-black and porous. Sometimes, the bone seems to "weep" droplets of pus as it oozes from the haversian canals. All of our patients presented these clinical signs. Roentgen evidences of infection were demonstrable in Case I and Case III. In Case II, the denuded and infected bone appeared normal roentgenographically. The difference in the clinical and roentgen observations in this patient is not unusual. Roentgen manifestations of infection frequently develop much later than the clinical signs. Roentgenographic evidences of malignant bone invasion occur still later.

The therapeutic procedures varied in each individual. One patient, Case II, had high voltage radiation (200 kv.) alone. Another, Case I, received intermediate voltage (135 kv.) and high voltage (200 kv.) radiation. The third patient, Case III, was treated with radium and intermediate voltage (135 kv.) rays. The total dose employed in each instance varied considerably. In spite of these differences, each patient died of an intracranial infection.

DISCUSSION

A review of the literature pertaining to the treatment of carcinoma of the scalp throws little light upon the development of the intracranial infections observed above. Though bone infections and necrosis have been reported[3,5,7] following irradiation of the calvarium, we could find nothing simulating the complications encountered in our patients. Conferences with colleagues[10] also failed to reveal similar experiences, though comparable doses of radiation were being employed for scalp cancers in the presence of infected and denuded bone. According to these men their results, in lesions similar to the ones we treated, were uniformly good irrespective of the type of therapy employed.

For years these lesions were successfully handled in our hospital by a combination of irradiation plus wide desiccation. By this method the pericranium and bone were purposely destroyed. Subsequently, covering of the exposed bone was facilitated by burr holes which stimulated granulation tissue proliferation and healing. Because such methods seemed extreme, we hoped that carcinolytic doses of radiation might prove equally successful and less mutilating. In view of past experiences in treating patients with brain tumors, we felt no hesitancy in exposing the head to large quantities of radiation. By decreasing the target-skin distance to 18 cm., we hoped to protect the bone and brain still further, and at the same time to increase the absorption of radiation in the superficial tissues. In view of past experiences with infections following the combined method for treating carcinomas of the scalp, no unusual methods for controlling infection seemed necessary.

We are not prepared to answer the question as to why our patients developed intracranial infections. Certain observations in the literature relative to this problem, however, seem to merit discussion.

Ewing[4] has called attention to the peculiar susceptibility of the blood vascular system of bone to strangulation by irradiation. That such changes render membranous bone unusually fertile soil for bacterial invasion and necrosis has been amply demonstrated.[1,2,4,8,11] One patient in our group, Case III, developed bone necrosis. All three, however, had clinical, operative and histologic evidence of bone infection.

Normally, the spread of infections in the

FIG. 15. Case II. Section of bone showing, in the haversian canal, the presence of an inflammatory reaction at *B* with connective tissue formation and a vessel which is occluded. The vessel wall is distinctly thickened showing evidence of previous phlebitis at *A*.

body is limited by inherent protective mechanisms of the host. Most men agree that small doses of radiation enhance these protective forces. Large doses, however, impede rather than support them. It seems reasonable to believe, therefore, that the carcinolytic doses of radiation employed in our patients produced enough destruction of the normal immunologic barriers to infection to allow the spread of infection from the cranium by retrograde thrombophlebitis (Fig. 15). The meninges becoming infected, few barriers remained to prevent extension into the intracranial tissues. It is of interest to note that the most severe infections occurred in those patients (Cases I and III) who received the greatest amount of radiation. It is only fair to state, however, that both these patients had streptococcic infections whereas the third individual (Case II) had a staphylococcic infection which remained localized.

In the light of recent experiences, the brain can no longer be considered insensitive to radiation. Reflex changes,[6,9] cerebral hypoplasia,[3] vascular changes and glial degeneration reported in the literature bear ample testimony to this fact. The question arises, therefore, were the brain changes observed in our patients due to irradiation plus secondary infection? We have been assured by Dr. B. J. Alpers that the findings were primarily due to infection with little evidence present to suggest brain degeneration of the type seen following irradiation.

From the above experiences and observations, the question arises as to what should be the method of choice in the treatment of large carcinomas of the scalp. Does irradiation have a place in the treatment of this form of malignancy? If so, how should the problem of infection be handled? Or is surgery, either by electrothermic methods or scalpel, the safest procedure? We do not know the answer to the problem. We would hesitate, however, to employ irradiation in the manner described above without warning the patient's family as to the seriousness of possible complications. We believe more care should be exercised to control infection. We do not believe burr holes should be made into denuded cranial bones until all evidences of infection have been lacking for months.

SUMMARY

1. We have reported three patients with carcinoma of the scalp who died following irradiation.

2. In each instance, the fatal complication occurred as the result of an intracranial infection.

3. Complete post-mortem studies in two cases have been recorded.

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DISCUSSION

Dr. Cornelius G. Dyke, New York City. I have enjoyed listening to this paper and it is very timely that the authors call attention to these 3 cases. Of course, it is extremely difficult to be certain that the irradiation had something to do with and was causative in producing death in their patients by an infectious process, but I have also encountered some clinical and experimental material that leads me to believe that radiation when given in large doses may decrease the resistance of the tissues.

We have had several patients who during the roentgen treatment of a glioma developed an epidural abscess several weeks or months after the operation. In addition to these cases, we have experimented and treated 31 patients in the operating room with rather large doses of roentgen rays delivered at one sitting. These patients received from 2,000 to 3,000 r, 200 kv. (peak), which was rather intensive radiotherapy. Five of these 31 patients died of infections. That number is altogether too great for a hospital in which good aseptic technique is used and a large amount of brain surgery is done.

In addition to those 5 patients, a number of monkeys were irradiated with fairly large doses of roentgen rays, and 3 out of 10 monkeys developed infections and died of meningitis or cerebral abscess.

Therefore, from these various experiences, my feeling is that radiation in large doses apparently does interfere with the normal protective processes in the body and that some patients so treated are probably a bit more liable to infection and to succumb thereto than if they had not been treated in this manner.

I have one slide I would like to show (slide). When giving doses around 1,500 to 2,500 r in a rather short period of time, it is also well to remember that over a number of years this may have a definite effect on the brain. For instance, here is a slide showing the brain of a patient which had received 80 or 90 H.E.D. over a period of years. This patient from Berlin, reported by Markiewicz, subsequently developed blindness, convulsive attacks, and also had a large ulcer in the scalp and necrosis of the occipital bone. When this patient came to autopsy, I think it was somewhere in the neighborhood of four years after the last roentgen treatment was given, the medulla, and occipital and parietal lobes of the brain showed hemorrhagic necroses. Within the areas of necroses there were decreased reactions of the interstitial tissue and a deposit of homogeneous substances was noted which corresponded to Alzheimer's "colloid degeneration." The effects of irradiation on the brain, therefore, may become manifest five to fifteen years after treatment and prove fatal. A number of monkeys which were irradiated at the Neurological Institute did not show any immediate effect but later on did develop evidence of degenerative changes in the brain.

WEAK RADIUM NEEDLE TECHNIQUE IN CARCINOMA OF THE CHEEK*

By CHARLES L. MARTIN, E.E., M.D., F.A.C.R.
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THE interesting reports of Cade[1] and his associates from the Westminster Hospital in London, published some ten years ago, caused us to become interested in the use of needles containing very small amounts of radium as a substitute for radon seeds. A description of the first two needles adopted together with their advantages and disadvantages was published in 1932[2] and the three sizes which have been used for the past six years were described in 1935.[3] These needles have active lengths of 0.5, 2.0 and 4.0 cm. The small one contains 0.6 mg. of radium and the others contain 0.6 mg. per centimeter of active length. This type of loading was adopted because the reports of the British workers indicated that such needles placed parallel to one another at 1.0 cm. intervals in epidermoid carcinoma in the mouth for seven days should produce a complete regression of the disease. At first it seemed only necessary to place them around the periphery of the tumor and some excellent regressions were produced in this manner, but since in most instances these regressions were not permanent, it became evident that a better distribution should be worked out. Much of our earlier work was done on an empirical basis, but figures published by Quimby[4] in 1935 have helped us to rationalize our procedures. Although larger masses have been handled successfully this paper will be limited to a discussion of flat lesions having a thickness of 1.0 cm. or less. Such tumors are frequently encountered on the mucosa of the cheek, floor of the mouth, palate, lip and face. When thick polypoid masses are encountered, the projecting portions are removed with a radio knife loop so that the remaining tumor has the proper thickness. Early observations indicated that the best results followed the implantation of parallel needles into the base of the neoplasm so arranged that the active portions extended well outside its borders. In most instances extra needles were implanted in normal tissue outside the edges of the tumor. Such patterns made it impossible to use the tumor volume calculations proposed by Martin and Quimby[5] because the sources of radiant energy were not entirely within the malignant tissue.

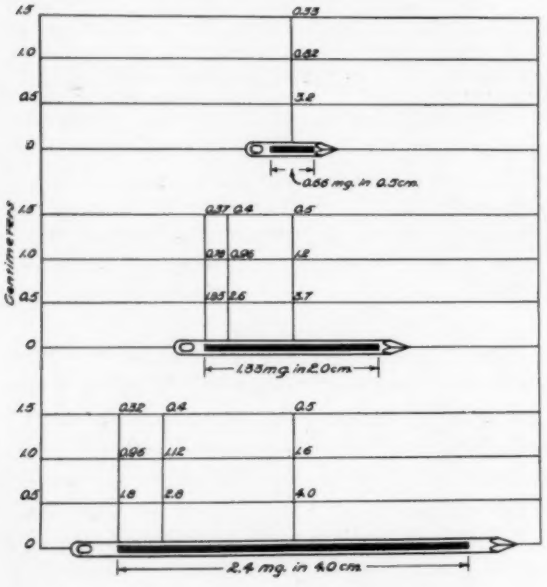

FIG. 1. Chart indicating effective threshold erythema doses at various distances from the weak radium needles when they are left in the tissues for seven days (168 hours).

Quimby has recently suggested that we depend entirely on point determinations in our work using her tables for needles of various lengths published in 1935. The chart shown in Figure 1 was constructed from these tables with some minor correc-

* Read at the Twenty-Fourth Annual Meeting, American Radium Society, St. Louis, Mo., May 15–16, 1939.

tions recently suggested by Quimby. The figures above each needle represent the number of threshold erythema doses delivered in the tissues at the locations indicated when the needles remain in position for 168 hours (seven days) which we have adopted as our standard time of treatment.

The data supplied by this chart can be used quickly and no elaborate calculations are necessary. The pattern used for a tumor measuring 4.0×1.5 cm. is shown in Figure 2 where only 2.0 cm. needles are used. At the point *A* the total radiation from the adjoining needles is 3.7×2 or 7.4 threshold erythema doses. The needles placed 1.5 cm. from this point each furnish 0.5 T.E.D. or a total of 1.0 T.E.D. The more distant needles deliver so little radiation that they can be neglected. The combined effect therefore amounts to 8.4 T.E.D. It is evident that with such an arrangement, the least radiation is delivered along the lower and upper edges and for this reason we have found it wise in some instances to place long needles at right angles to those shown in the sketch just above the heads and below the points. Such a plan delivers a dose of 7 to 8 T.E.D. fairly evenly throughout the tumor and the effective radiation falls within the range advocated as curative by Martin and Sharp[6] for intraoral lesions.

In our original article it was contended that the weak needles were more efficient than radon seeds used in accordance with the plan described by Martin and Sharp and the above calculations seem to bear this out. In Figure 2 the total amount of radium used amounts to almost 8.0 mg., whereas the above authors advocate 20.0 mc. as the amount of radon needed to deliver 7 T.E.D. to a tumor having a long diameter of 4.0 cm.

Although our experience with radon seeds is limited, we are led to believe that our plan is less likely to produce sloughing and bone damage because the active sources are spread out over a much larger area and in the near future we plan to publish statistics giving the incidence of these complications in our clinic.

It must be admitted that the technique of implanting and anchoring needles properly in the mouth constitutes one of the greatest objections to the method and some skill must be acquired before satisfactory patterns can be placed in the more irregular lesions. This has been forcibly impressed on us through observing the awkwardness of surgical interns when they first become radiological residents. Fortunately, the needles can be removed and replaced until they are satisfactorily arranged and this in itself constitutes an advantage over the radon seed technique unless one uses removable seeds.

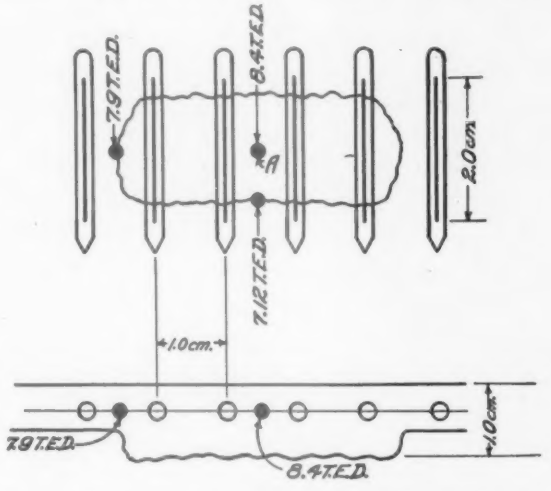

FIG. 2. Drawing illustrating the distribution of 1.33 mg. needles for the treatment of a tumor measuring 4.0×1.5 cm. The tissue dose averages from 7 to 8 T.E.D. throughout the tumor and the total amount of radium used is 8.0 mg.

A needle of each type and the instruments employed in intraoral work are illustrated in Figure 3. The needles are placed in pure carbolic acid for ten minutes and then transferred to 70 per cent alcohol. They are then threaded with dental floss sutures which are tied in the middle so as to leave the two ends free and are returned to the alcohol for at least an hour before they are used. The hands of the technician who prepares the needles are scrubbed and sterilized before this procedure is carried out. The dental floss is obtained on 150 yard spools which have been sterilized and

placed in closed bottles. This suture material is quite strong and since it is waxed it does not tangle easily and is tolerated well by the tissues of the mouth. A sterile solution of butyn and epinephrine furnished in 4 oz. bottles keeps indefinitely and produces an excellent local anesthesia for intraoral work. Since any amount can be withdrawn through the rubber stopper in the bottle as it is needed, none of the solution need be wasted. After each needle is inserted with the heavy forceps and forced below the surface with a countersinking instrument, the short end of the suture is threaded into the eye of one of the small curved skin needles and a stitch is taken through normal mucous membrane and tied. The knot is always tied on the side of the stitch toward the needle and the long end of the suture is brought out through the corner of the mouth so that it may be tied into a tag attached to the forehead after the work is completed. When the knot is properly placed it is only necessary to cut the stitch on the side away from the knot to assure the easy removal of the needle by means of the long end of the suture. An instrument consisting of a bar with a

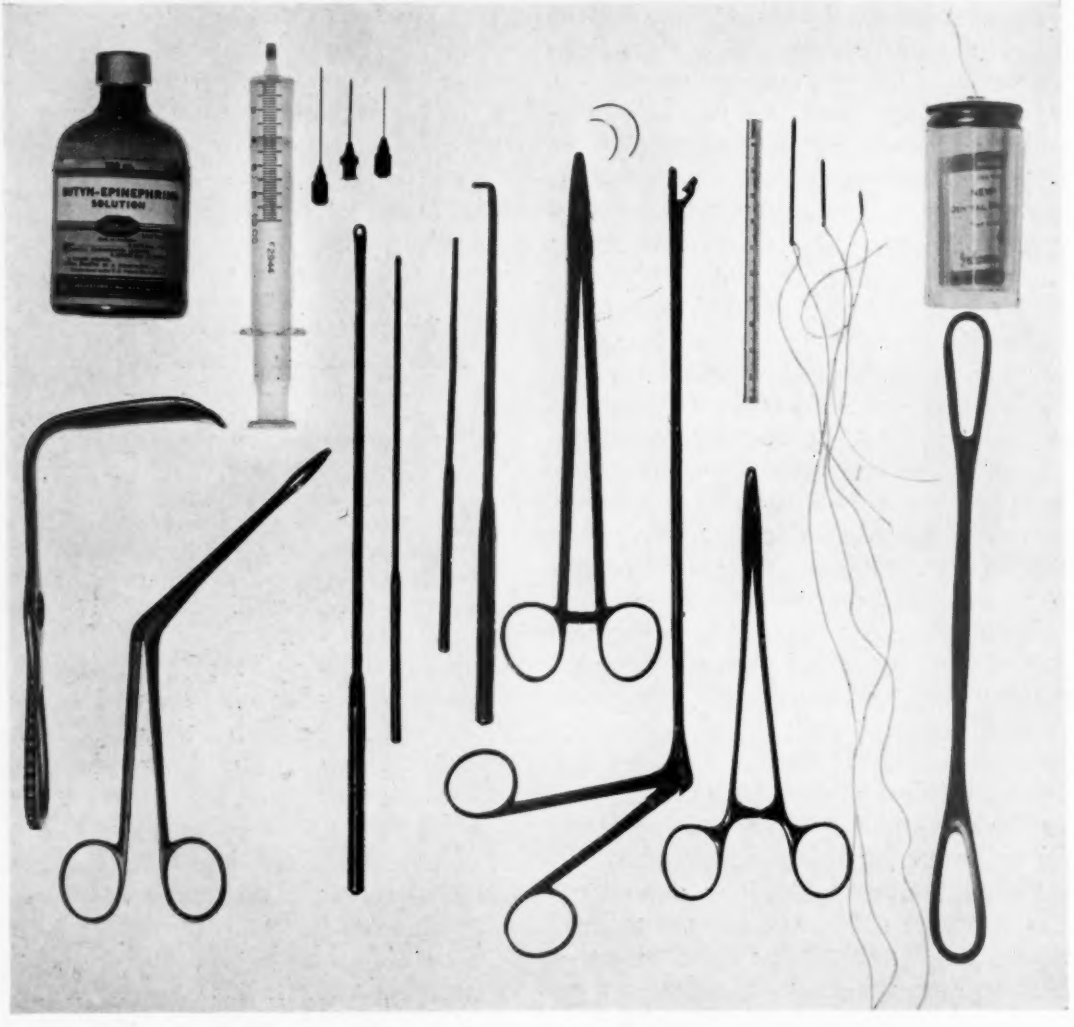

FIG. 3. Weak radium needles of each type threaded for use, anesthetic, dental floss and instruments utilized in intraoral work.

Y-shaped lower end has been found very useful in placing knots on the base of the tongue, in the soft palate, the anterior pillar and other locations not readily accessible to the operator's fingers. A pair of sewing forceps with a hole in the top of one jaw through which the curved needle may be passed greatly facilitates the placing of stitches in locations which are difficult of access. The long instrument with a round hole in its lower end is sometimes used in removing needles inserted in the back of the mouth with the points extending in an anterior direction. By threading the long suture through the hole and placing the end of the instrument in the throat, the tension on the thread can be exerted in a line parallel to the long axis of the needle. The biopsy forceps illustrated in Figure 3 have proved valuable because they possess very sharp cutting surfaces which make it possible to remove a fairly large specimen quickly. The resulting wound is immediately coagulated with a high frequency electrode and the field is free of hemorrhage during the implantation procedure. Since the care of the patient with radium needles in the mouth has been discussed in another article[3] it will not be considered here.

CANCER OF THE CHEEK

The weak needles have been used with considerable success in cancer of the skin, tongue, palate, parotid, vulva, vagina and cervix, but cancer of the cheek has been selected to illustrate the results obtained because it constitutes the most common as well as the most favorable intraoral carcinoma seen in our clinic. The frequency of occurrence is probably due to the prevalence of "snuff dipping" among the women and tobacco chewing among the men in the rural districts of the Southwestern States. Martin and Pflueger[7] have described the poor results obtained in the treatment of cancer of the cheek with surgery alone and have collected a series of 79 cases reported by Warren, Brewer, Bradfield and Davis in which not a single operative cure was obtained. The reader is referred to this article for a survey of the rather scanty surgical literature.

Our first case was treated in 1930 and a survey of the 35 patients treated from 1930 to 1936, inclusive, is shown in Table 1. All stages of the disease are included and for that reason the results cannot honestly be compared with those obtained in operable

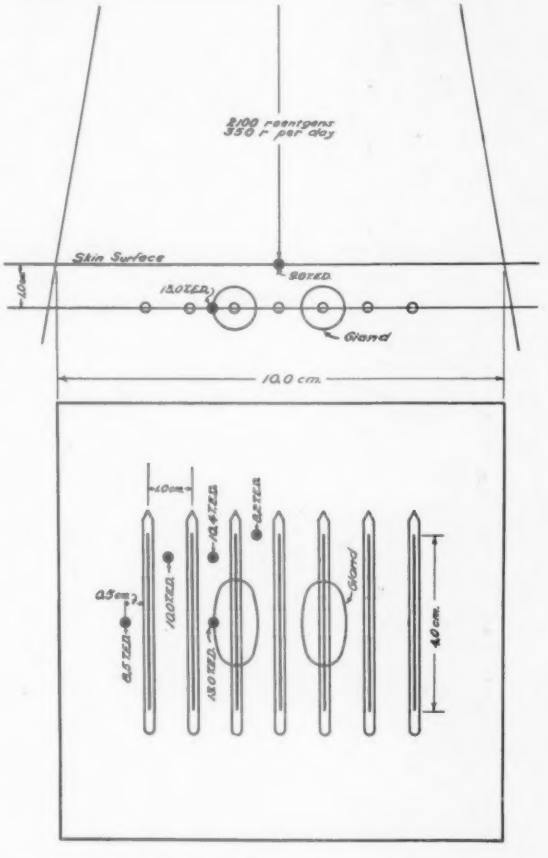

Fig. 4. Drawing illustrating the combined use of roentgen rays and weak radium needles used simultaneously for seven days in the treatment of the cervical lymphatic area when glandular metastases have appeared. The effective dose varies from 10 to 13 T.E.D.

cases alone. Several changes in technique have been made and the more recent results are apparently much better than those obtained in the beginning. At first complete reliance was not placed on the implanted needles and several erythema doses were added using radium capsules held against the mucosa by means of lead strips.

Fig. 5. Three cases of proved carcinoma of the cheek which have remained well and free of cancer for six years following the use of weak radium needles. They are Cases xv, xiv, and ix reading from above as listed in Table 1. The lower case was an epidermoid carcinoma, Grade 2, and the others were both epidermoid carcinomas, Grade 1.

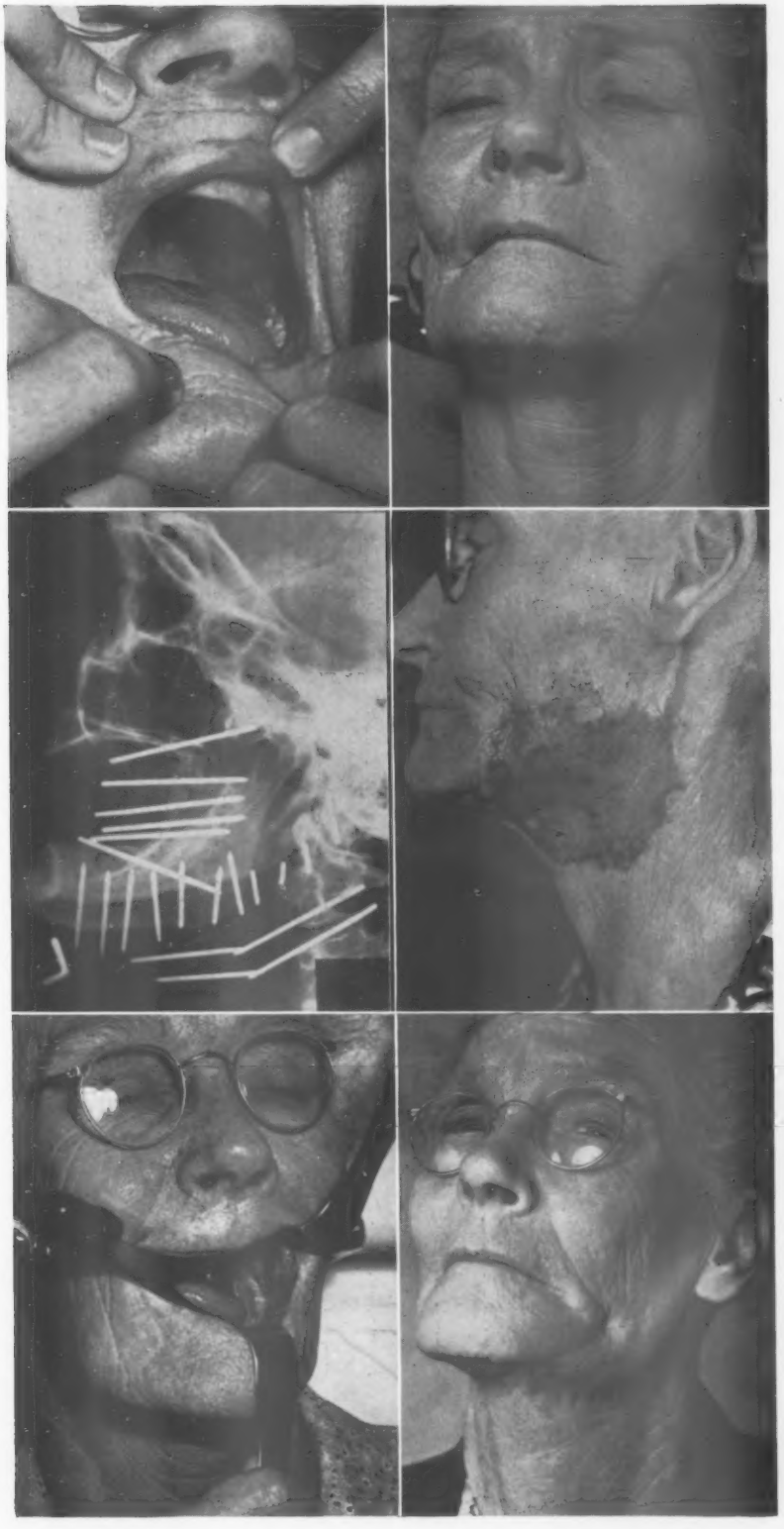

Fig. 6. Large epidermoid carcinoma, Grade 1, of cheek with perforation and multiple submental and submaxillary lymph nodes treated with the combined radium needle implantation and roentgen therapy illustrated in Figure 4. The epithelitis healed rapidly and the lower photographs reveal no visible or palpable evidence of carcinoma seven months after the treatment was given.

TABLE I

Year	Case	Primary Lesion		Pathology	Extension	Treatment		Results
		Size cm.	Location			Interstitial—7 days	External	
	I. D.S.C.	2.0	Mid cheek	Epidermoid cancer, Grade 2	No glands	7—0.6 mg. needles (200 mg-hr. contact)	1100 mg-hr. pack 600 r x-ray	Well 9 yr.
1930	II. J.D.C.	3.5	Gingiva and cheek	Epidermoid cancer, Grade 3	2 Submax. glands	10—0.6 mg. needles (520 mg-hr. contact)	1100 mg-hr. pack 2 areas	Local healing, glands growing at 5 mo.
	III. J.W.D.	2.5	Gingiva and cheek		No glands	6—0.6 mg. needles		Untraced
	IV. B.F.H.	2.0	Gingiva and cheek	Epidermoid cancer, Grade 3	No glands	9—0.6 mg. needles		Extension into jaw at 2 mo.
	V. J.A.S.	2.5	Gingiva and cheek	Epidermoid cancer, no grade	No glands	9—0.6 mg. needles	2400 mg-hr. pack	Submax. glands 8 mo. later
1931	VI. W.B.G.	6.0	Entire cheek	Epidermoid cancer; no grade	Large submax. gland	8—1.33 / 7—0.6 cheek; 4—1.33 gland	2000 mg-hr. pack 600 r x-ray	Local healing, died of recurrence 10 mo. later
	VII. C.C.M.	3.5	Carcinoma mouth, cheek and nose	Epidermoid cancer, Grade 2	No glands	11—0.6 mg. needles 1—1.33 mg. needles	600 r x-ray	Local healing, died 1 yr. later
	VIII. Mrs. T.P.R.	6.0	Entire cheek	Epidermoid cancer, Grade 2	No glands	9—1.33 mg. needles 8—0.6 mg. needles	3000 mg-hr. pack 300 r×6, each side	Local healing, deep recurrence in 10 mo.
	IX. W.L.N.	3.5	Gingiva and cheek	Epidermoid cancer, Grade 2	Small glands?	16—0.6 mg. needles 7—1.33 mg. needles	3000 mg-hr. pack 600 r x-ray	Well 6½ yr.
	X. T.F.	3.5	Gingiva and cheek	Epidermoid cancer; no grade	1 submax. gland	12—0.6 mg. mouth 4—1.33 gland (300 mg-hr. contact)	2400 mg-hr. pack 600 r x-ray	Local healing, died 5 yr. later, recurrence
1932	XI. J.M.P.	3.0	Gingiva and cheek with perforation	Epidermoid cancer, Grade 1	Large submax. gland	8—0.6 mg. needles 2—1.33 mg. needles	3000 mg-hr. pack 600 r x-ray	Temporary regression, died with deep recurrence
	XII. D.J.S.	2.5	Gingiva and cheek	Epidermoid cancer, no grade	No glands	10—0.6 mg. needles	To jaw 300 r×11	Local healing, recurrence in neck at 6 mo
	XIII. J.C.N.	5.0	Whole cheek with perforation	Epidermoid cancer, Grade 2	No glands	4—0.6 mg. needles 11—1.33 mg. needles	3000 mg-hr. pack 600 r x-ray	Large clean hole in cheek at 8 mo., untraced since
	XIV. M.A.F.	4.5	Lower cheek with perforation	Epidermoid cancer, Grade 1	No glands	9—0.6 mg. needles 1—1.33 mg. needles 2—2.4 mg. needles	3100 mg-hr. pack 600 r x-ray	Well 6 yr.
	XV. W.A.Y.	2.5	Gingiva and cheek	Epidermoid cancer, Grade 1	No glands	14—0.6 mg. needles	3600 mg-hr. pack 600 r x-ray	Well 6 yr.
	XVI. Mrs. J.W.	2.0	Cheek	Adenocarcinoma, mucous type	No glands	7—0.6 mg. needles 1—1.33 mg. needles	3600 mg-hr. pack 600 r x-ray	Well 5 yr. 8 mo.
	XVII. Mrs. R.L.S.	3.5	Gingiva and cheek with perforation	Epidermoid cancer, Grade 2	Large submax. gland	6—0.6 mg. needles 9—1.33 mg. needles	600 r x-ray	Local healing, extension in neck
1933	XVIII. Mr. L.L.R.	2.0	Cheek	Epidermoid cancer, Grade 2	No glands	8—0.6 mg. needles 2—1.33 mg. needles	3600 mg-hr. pack 600 r x-ray	Well at 6 mo., untraced since
	XIX. Mrs. D.W.O.	2.0	Gingiva and cheek	Epidermoid cancer, Grade 3	Large cerv. glands	8—0.6 / 1—1.33 cheek; 6—2.4 glands	3600 mg-hr. pack	Improved for 4 mo., more cervical extension thereafter
	XX. A.G.D.	6.0	Entire cheek	Epidermoid cancer, Grade 1	No glands	16—1.33 mg. needles 6—0.6 mg. needles	3000 mg-hr. pack 600 r x-ray	Complete healing, died 3 yr. later, cause unknown

	XXI. H.E.M.	3.5	Gingiva and cheek	Epidermoid cancer, no grade	No glands	9—0.6 mg. needles 3—1.33 mg. needles	3000 mg-hr. pack 600 r x-ray	Complete healing, died 2 yr. later, cause unknown
	XXII. Mrs. C.W.	3.5×4.5	Entire cheek	Epidermoid cancer, no grade	Large subment. gland	7—1.33 } cheek 4—0.6 } 3—1.33 gland (500 mg-hr. contact)	600 r x-ray	Local healing, more cervical extension at 4 mo.
1934	XXIII. Mrs. M.C.	5.0	Entire cheek	Epidermoid cancer, Grade 1	No glands	10—2.4 mg. needles 6—1.33 mg. needles	300 r × 3 x-ray	Complete healing, no recurrence, died of another disease 5 yr.
	XXIV. J.C.S.	3.5×2.0	Cheek	Epidermoid cancer, Grade 1	No glands	6—1.33 mg. needles 6—0.6 mg. needles	300 r×5 x-ray to each side	Well 5 yr., some leukoplakia present
	XXV. G.A.P.	2.5	Cheek	Epidermoid cancer, Grade 4	Large subment. gland	8—0.6 } 3—1.33 } cheek 2—2.4 } 3—2.4 gland	300 r×6 x-ray to neck	Local healing, other cervical glands at 3 mo.
1935	XXVI. G.D.	6.0	Entire cheek	Epidermoid cancer, Grade 1	Submax. gland	10—1.33 mg. needles 11—2.4 mg. needles	350 r×6 x-ray to neck	Complete local healing, more cervical extension in 6 mo.
	XXVII. J.F.Mc	3.5	Ant. pillar and cheek	Epidermoid cancer, Grade 2	No glands	7—0.6 mg. needles 7—1.33 mg. needles	350 r×6 x-ray to neck	Small slough resected at 8 mo., well 4 yr.
	XXVIII. W.F.T.V.	3.5	Cheek	Epidermoid cancer, Grade 2	Large submax. gland	4—1.33 } cheek 7—2.4 } 4—1.33 gland	350 r×5 x-ray to neck	Well 4 yr. 3 mo.
	XXIX. A.L.W.	3.5	Ant. pillar and cheek	Epidermoid cancer, Grade 2	Subment. gland and bone	7—0.6 } 4—1.33 } cheek 3—2.4 } 3—2.4 gland	350 r×5 x-ray to neck	Very little improvement at 3 mo., untraced
1936	XXX. Mrs. W.H.M.	3.0	Cheek	Epidermoid cancer, Grade 2	? Glands	7—0.6 mg. needles 4—1.33 mg. needles	350 r×6 x-ray to neck	Well 2 yr. 10 mo.
	XXXI. Mrs. J.T.D.	3.5	Cheek	Epidermoid cancer, Grade 1	No glands	1—2.4 mg. needles 5—1.33 mg. needles 6—0.6 mg. needles	350 r×6 x-ray to neck	Well 3 yr. 3 mo.
	XXXII. J.A.H.	2.5	Cheek	Epidermoid cancer, Grade 2	No glands	3—0.6 mg. needles 5—1.33 mg. needles	350 r×6 x-ray to neck	Well 2 yr. 5 mo.
	XXXIII. C.W.	6.0	Cheek and lip	Epidermoid cancer, Grade 1	No glands	3—1.33 } 4—0.6 } lip	300 r×12 x-ray to cheek and lip	Well 2 yr. 8 mo.
	XXXIV. S.P.	3.0	Ant. pillar, cheek and gingiva	Epidermoid cancer, Grade 2	No glands	8—1.33 mg. needles 6—0.6 mg. needles		Local healing, deep recurrence at 5 mo.
	XXXV. Miss D.P.	2.0	Cheek	Epidermoid cancer, Grade 1	No glands	6—1.33 mg. needles	350 r×5 x-ray to neck	Well 2 yr. 9 mo.

This extra radiation was soon found unnecessary and was abandoned.

Although the local improvement was encouraging from the start, it soon became evident that most of the failures resulted from the improper care of cervical metastases. An attempt was made to augment single erythema doses of 200 kv. roentgen rays with 2 or 3 erythema doses delivered with a small radium pack made by placing two heavily filtered 50 mg. radium capsules on a balsa wood block designed to hold them at a distance of 2.0 cm. from the skin. Even when this pack remained in place for thirty-six hours the dose 1.0 cm. below the skin obtained with the combined treatment amounted to less than 3.0 T.E.D. and the results were indifferent. In 1933 a few of the glands were implanted with needles, using a dosage similar to that applied to the local lesion but although improvement occurred it soon became evident that 7.0 T.E.D. would not control metastatic carcinoma in lymph nodes. Divided doses of deep roentgen rays were then added to the implanted areas in the neck until it was learned empirically that 2,100 r might be given while the needles were in place at the rate of 350 r per day without producing irreparable skin damage. This combined method was adopted because Quimby and Pack[8] showed a good many years ago that the combined effect of heavily filtered roentgen-ray and radium doses on the skin is less than that of equal amounts of either roentgen rays or radium rays alone. The roentgen therapy was administered at 220 kv., with 20 ma., a filter of 2.0 mm. of copper and 1.0 mm. of aluminum, a target-skin distance of 50 cm. and areas measuring 10.0 cm. on a side. The dosage obtained is illustrated in Figure 4. The threshold erythema doses accredited to the radium needles may be obtained from Figure 1 and since 525 r produces 1 T.E.D. at a depth of approximately 2.0 cm., 4.0 T.E.D. may be added to the radium dosage at each point. The resulting figures show that the glands and their surrounding lymphatics receive from 10 to 13 T.E.D. That such a plan is effective has been proved in a previous paper,[9] and the only patient in this series with a cervical node remaining well for more than three years (Case XXVIII) was so treated. The entire procedure is illustrated in Figure 6. This patient had a large carcinoma extending entirely through the cheek, and several hard non-tender glands were

TABLE II

CURED CASES OF CARCINOMA OF CHEEK

Patient	Age	Size cm.	Pathology	Glands	Tobacco	Free of Disease
I D.S.C.	46	2.0	Epidermoid cancer, Grade 2	None	Smoked 20 yr.	9 yr.
IX W.L.N.	54	3.5	Epidermoid cancer, Grade 2	None	Chewed years	6½ yr.
XIV M.A.E.	52	4.5	Epidermoid cancer, Grade 1	None	Chewed 30 yr.	6 yr.
XV W.A.Y.	57	2.5	Epidermoid cancer, Grade 1	None	Chewed years	6 yr.
XVI Mrs. J.W.	53	2.0	Adenocarcinoma	None	Poor plate	5 yr. 8 mo.
XXIII Mrs. M.C.	48	5.0	Epidermoid cancer, Grade 1	None	Snuff dipper	5 yr.
XXIV J.C.S.		3.5×2.0	Epidermoid cancer, Grade 1	None	Chewed years	5 yr.
XXVII J.F.Mc.	76	3.5	Epidermoid cancer, Grade 2	None	Chewed 45 yr.	4 yr.
XXVIII W.T.F.V.	68	3.5	Epidermoid cancer, Grade 2	Submax. gland	Chewed years	4 yr. 3 mo.
XXX W.H.M.	73	3.0	Epidermoid cancer, Grade 2	None	Snuff dipper	2 yr. 10 mo.
XXXI Mrs. J.T.D.	54	3.5	Epidermoid cancer, Grade 1	None	Denies snuff	3 yr. 3 mo.
XXXII J.A.H.	74	2.5	Epidermoid cancer, Grade 2	None	Smoked years	2 yr. 5 mo
XXXIII Miss C.W.	50	6.0	Epidermoid cancer, Grade 2	None	Snuff dipper	2 yr. 8 mo.
XXXV Miss D.P.	60	2.0	Epidermoid cancer, Grade 1	None	Snuff dipper	2 yr. 9 mo.

palpable in the submaxillary and submental regions. The needles were placed so as to irradiate the involved nodes as well as the lymphatics beyond them. A dose of 2,100 r was given to an area measuring 10.0 cm. on a side while the radium needles were in place. The epithelitis produced on the skin healed in rapidly and no evidence of carcinoma can be detected either in the mouth or neck at the end of seven months. So many patients have responded well to this form of treatment that it has been adopted as a routine procedure in our office for all cases with intraoral carcinoma even when no palpable nodes are present. In a busy clinic where economic factors must be considered a technique which can be finished in one week has much to commend it.

Although the neck was efficiently treated in only the more recent cases reported in Table I the results are encouraging. A list of the 14 traced patients in which we have every reason to believe that a cure was produced is given in Table II. Cases XVIII, XX and XXI may also have been cured but they are omitted from Table II because they could not be properly followed up. Although half of these cured patients have not as yet been free of malignant disease for five years, several observers have stated that cancer of the cheek very rarely recurs when it remains well for three years and it seems fair to claim a salvage of 40 per cent in the series of 35 cases treated. Since some of these patients will probably die of other causes before the five year period has expired, our figure of 40 per cent represents approximately the same number of cures as the 30 per cent five year salvage reported by Martin and Pflueger.

SUMMARY

1. Careful dosage calculations show that 7 to 8 threshold erythema doses can be delivered uniformly to intraoral tumors by means of weak radium needles placed parallel to one another in and around the lesion for a period of seven days.

2. This plan is easily applied in the cheek and a relatively small amount of radium is needed.

3. The 10 to 13 T.E.D., which in our opinion is needed to permanently control metastatic cervical lymph nodes, can be safely given with a combination of weak radium needles and divided doses of deep roentgen rays in a period of seven days.

4. In a series of 35 unselected cases of carcinoma of the cheek (mucosal portion) treated with the above plan 40 per cent appear to be well for periods of two and a half to nine years.

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DISCUSSION

Dr. Harold G. F. Edwards, Shreveport, La. I have enjoyed Dr. Martin's paper very much. It brings out one point and that is that with radium therapy there are many techniques, like the railroads, there are many running into St. Louis and all of them have brought you here safely. I think all of us probably have a little different type of technique.

I have been using platinum needles since

early 1932 and my set-up is a little different from that of Dr. Martin. My 27 mm. needles are 1 mg. of radium with filtration of 0.5 mm. platinum and an active length of 16 mm. While the 2 mg. needles are 44 mm. in length, the 3 mg. are 60 mm. and I have some 4 mg. which are 76 mm. More recently, because of the mail limitations on radon shipments, I have purchased the small platinum element implants devised by Dr. Pack.

The needles which I make use of as a rule are left in the epidermoid types of carcinoma for eight days. In a lip, making use of seven 1 mg. platinum needles, if the tumor isn't too extensive, they are left in eight days. If, on the other hand, the tumor is bulky, additional needles of 2 mg. are put in at the peripheral zones. Treated in this manner, we have not failed to secure primary healing and the patient has remained cured, many of them over a five year period.

I have found that the small Pack implant will work well in carcinoma at the base of the tongue when implanted, by a simple incision through the skin, just above the hyoid bone, under bloc infiltration; implantation is done through the trocar into the base of the tongue.

In using platinum needles in the oral cavity, I have not made use of sutures but rather have attempted to place the needles in such a fashion that they interlock and when so placed, we cross-tie them. I think that this causes less trauma and may solve the one problem which, in my opinion, is the one great cause of necrosis following interstitial irradiation: infection. I think that a great many of these sloughs we see following interstitial irradiation and heavy roentgen irradiation unquestionably come about because of secondary infection.

With regard to the metastatic nodes in the neck, first of all we must prove that the mode is carcinomatous. It is quite true that in a patient who has had a proved epidermoid carcinoma of the oral cavity and later develops an enlarged node it is usually malignant, but the procedure to prove it is such a simple one that we should not treat the patient until this is done. Furthermore, it offers us additional information as to whether or not this node has undergone some liquefaction and has started to break down. If it has, it presents quite a different problem.

I believe that by simple aspiration of a metastatic node and placing the material on a slide and crushing it and holding it up to the light, by just macroscopic evidence we are able to say in about 85 to 90 per cent that this is metastatic carcinoma. It presents a mealy appearance on the slide, somewhat as the old Bass-Watkins typhoid agglutination test did. Further study can be made immediately by staining with hematoxylin and eosin, finding the epithelial scales and in some instances the metastatic cells with many mitotic figures.

If the node is small and we feel sure it has not perforated the capsule, then I prefer to cut down on the node, using local anesthesia, and use the small Pack radium element implants. Previously I had been using radon. I believe that this is preferable to intensive roentgen therapy first and then needles immediately following; because we are treating only one small node and then we have preserved the skin and underlying structures so that if a subsequent node does develop, we can again attack it in the same manner and still preserve the structures in the neck, while if we have irradiated heavily, using rather large roentgen fields and follow with interstitial irradiation, we have almost closed the door to any future therapy.

When the node has perforated the capsule, which we feel is evidenced by fixation and liquefaction in the node, then I employ a method similar to Dr. Martin's: giving a daily fraction of 200 r, running up to approximately 3,500 r, and immediately under general anesthesia place the large needles, the 4 mg., which are 76 mm. in length, without regard to blood vessels, nerves or whatnot, deeply into the tissues and into the node where possible. These are left in eight to ten days and we may use as high as 50 mg. in this fashion if the distribution is wide enough. With regard to distribution, of course it is ideal to think of distribution with the idea of spheres, but this is almost impossible to achieve. I think Mrs. Quimby's tables have certainly given us a guide by which we should travel and without which we would probably have gotten into much trouble.

As for myself, I feel that it is much better to overdose rather than underdose because if you underdose you cannot go back and treat your patient again, whereas if you overdose, if there is some slough and the distribution has been wide enough, you will get rid of all carcinoma cells in most instances and your patient will be cured of his cancer, while underdosage will sooner or later mean a dead patient.

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THE RELATION OF MEAL TEMPERATURE TO GASTRIC MOTILITY AND SECRETION*

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THE gastric temperature was obtained with a series of three iron-constantan thermocouples passed into the stomach with the leads conducted to the potentiometer through one side of a partitioned or double-barrelled Miller-Abbott tube. The thermocouples were coated with bakelite varnish to protect them from the action of the hydrochloric acid in the stomach. The precision of this thermometer was within 0.2° F. as checked against a standard precision mercury thermometer.† The temperature was then continuously recorded on graph paper. The subjects were obtained from among patients in our practice who were found to be healthy after careful examination; and this included elimination of all those emotionally unstable or neurotic as well as those with organic disease. A fractional gastric analysis was done simultaneously with the recording of temperature so that its bearing on gastric motility might not be overlooked. The test meal for all motor and secretory studies was 3 ounces of barium sulphate dissolved in 250 cc. of 2 per cent Liebig's extract. Extractions of 10 cc. of stomach contents were made every fifteen minutes through the other barrel of the partitioned Miller-Abbott tube during the period of temperature recording and each experiment was terminated when the stomach was emptied, determined by the extraction method and by roentgenoscopic observation. Some subjects were studied in the morning after a fifteen hour fast and others were studied in the evening after a nine hour fast.

The first test was made with a meal at body temperature varying from 98–99° F. The findings were checked two or three times and the subject used for further study only if the results were consistent; in this way, we hoped to eliminate those in whom the presence of neuropsychic factors might have presented indeterminable variations.

At the next test, done usually after an interval of one week—after determining complete evacuation of the previous barium-Liebig meal—the temperature of the meal varied from 35–40° F. The third examination was made with a meal heated to 140–145° F. A few determinations were made with the meal at room temperature.

The secretory studies of the stomach comprised determination of free and combined hydrochloric acid by titration; total chlorides by the method of Wilson and Ball and the quantitative determination of pepsin by a slight modification of the Polland and Bloomfield method.

COMMENTS

In the 24 subjects used for these experiments, the gastric temperature varied from individual to individual much like the mouth and rectal temperature, extending from 97.4 to 99.6° F. The stomach temperature of each subject was noted continuously for fifteen minutes or more before ingestion of the various test meals. With the meal of 35° F., a marked immediate drop in gastric temperature occurred after ingestion, usually to 70–75° F. This drop in temperature strikingly demonstrates the capacity of the mouth, pharynx and esophagus to rapidly heat an ice-cold drink. While this rapid initial heating changes the gastric temperature from 35 to 70° F., the contents do not reach body temperature for thirty to forty minutes.

A hot drink taken at 145° F., which is as high as the average subject can tolerate,

† The thermocouples were made for us by Dr. A. N. Lucian, of the Research Physics Department, University of Pennsylvania.

* Read at the Thirty-Ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 20–23, 1938.

is cooled almost immediately on entering the stomach to 106–110° F. and reaches body temperature within fifteen to twenty minutes.

The differences in gastric motor reactions to meals of widely different temperatures seem interesting. The cold meal begins to leave the stomach almost immediately and rushes more rapidly than usual through the jejunum and ileum. The increased motility is most marked soon after ingestion corresponding to the period of greatest depression of gastric temperature; and as the gastric temperature returns slowly to normal, there develops a progressive slowing in gastric evacuation so that by the time the temperature of the gastric contents reaches normal (in thirty to forty minutes) motility is normal.

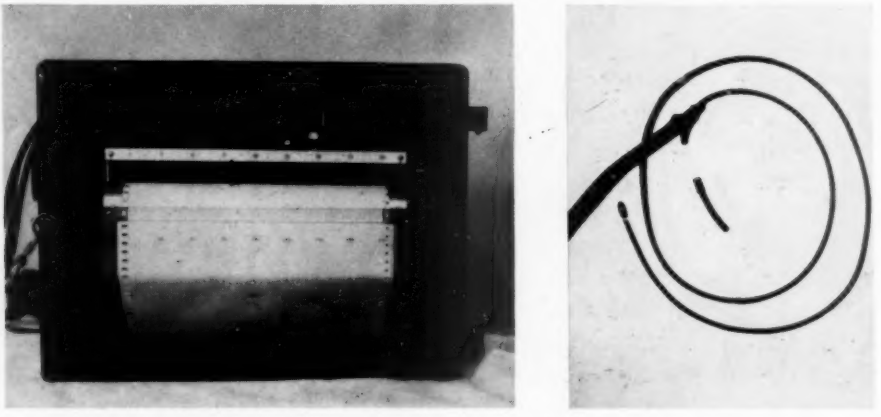

FIG. 1

The hot meal, on the other hand, is slower to leave the stomach at first, but soon empties normally or even slightly faster than normal. Since it is usually difficult to drink liquids heated higher than 40–50° F. *above* body temperature, it seems to take the stomach less time to bring this meal to body temperature than it does the cold meal imbibed at 65° F. *below* body temperature. It is probably for this reason that the intestinal patterns of the hot meal are not so markedly altered as by the cold meal.

No appreciable abnormal deviations were noted in the gastric secretory changes with the hot meal. With the cold meal, there is an actual depression of gastric secretions at first when the temperature is most markedly lowered; but within a shorter time than it takes for the gastric temperature to return to normal, gastric secretion is normally resumed. The curves in Figure 3 were plotted with correction of the dilution factors. They show the effect on the secretion of hydrochloric acid by test meals of different temperatures. Since more than normal gastric evacuation of the cold meal takes place soon after ingestion, the intestines are filled with more than the average amount of contents inadequately acted upon by the gastric juices. This might be one of the factors responsible for some of the diarrheas during the summer when the American custom of taking excessive ice-cold drinks is so generally followed.

DISCUSSION

John Hunter[1] in 1778 recorded stomach temperatures in cold-blooded animals and in 1878, Kronecker and Meyer reported experiments, using small maximum thermometers, which they permitted dogs and rabbits to swallow. When the thermometers were expelled from the rectum, the maximum temperature in the intestinal canal could be read. In order to determine the stomach temperature, they pulled the thermometer from the stomach by means of a

GASTRIC MOTILITY AND INTESTINAL PATTERNS AFTER HOT AND COLD MEALS

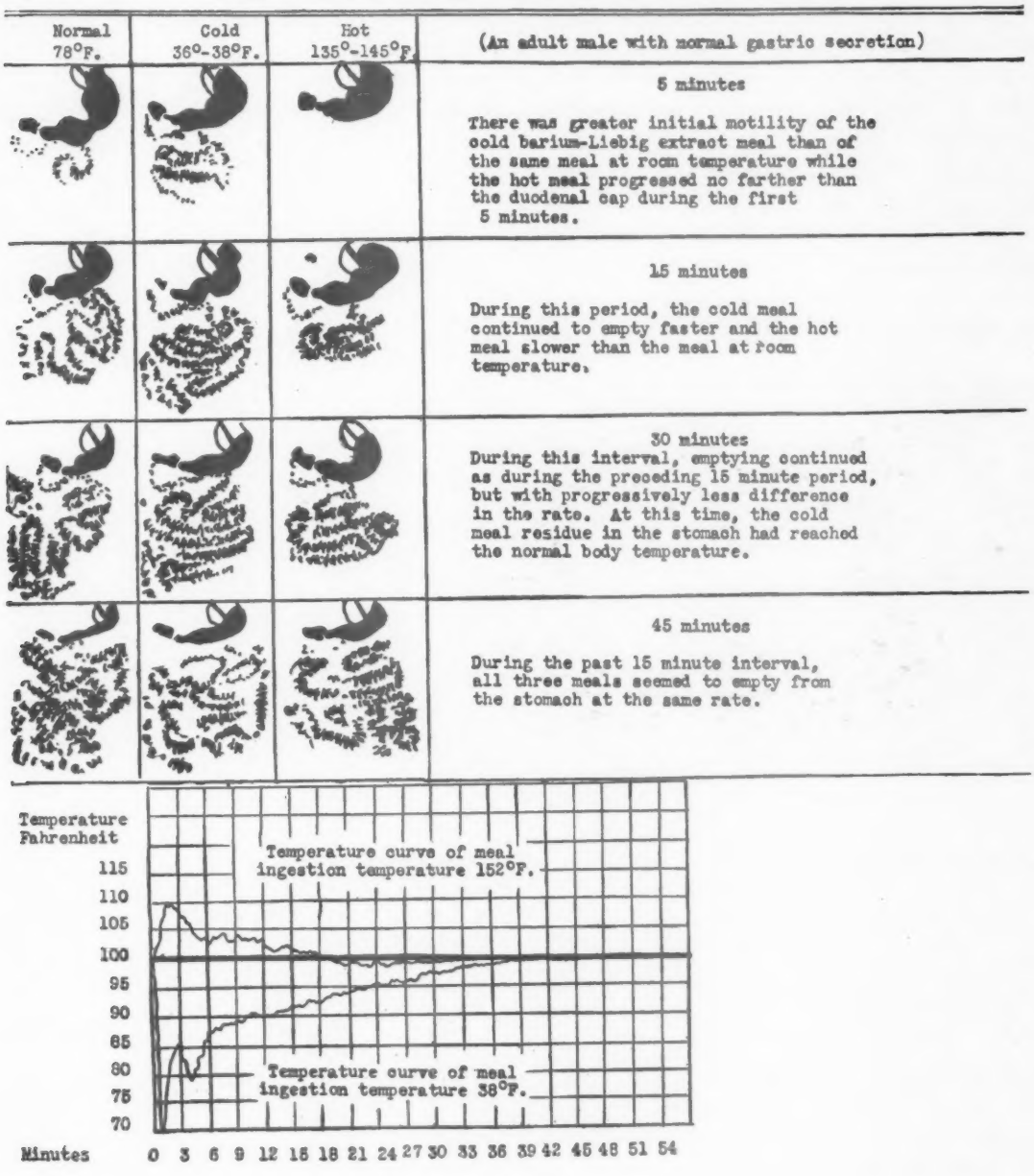
Normal 78°F.
Cold 36°-38°F.
Hot 135°-145°F.
(An adult male with normal gastric secretion)
5 minutes
There was greater initial motility of the cold barium-Liebig extract meal than of the same meal at room temperature while the hot meal progressed no farther than the duodenal cap during the first 5 minutes.
15 minutes
During this period, the cold meal continued to empty faster and the hot meal slower than the meal at room temperature.
30 minutes
During this interval, emptying continued as during the preceding 15 minute period, but with progressively less difference in the rate. At this time, the cold meal residue in the stomach had reached the normal body temperature.
45 minutes
During the past 15 minute interval, all three meals seemed to empty from the stomach at the same rate.
Temperature Fahrenheit
115
110
105
100
95
90
85
80
75
70
Temperature curve of meal ingestion temperature 152°F.
Temperature curve of meal ingestion temperature 38°F.
Minutes
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54

Fig. 2

thread. The temperature of the stomach was found to be 0.9° F. lower than the rectum. Beaumont (1825–1833) was the first to determine stomach temperature in man in his famous subject with the gunshot gastric fistula. The temperature in this case averaged 100.2° F. and varied from 98.1 to 100.8° F. Later Quincke (1889) determined the gastric temperature with a thermometer in a boy with a gastrotomy. In this instance, the gastric temperature was 0.27° F. higher than in the rectum. A similar experiment was carried out by Ranckin and Tigerstedt (1908) in a boy with a gastric fistula. They found the gastric temperature to be 0.36° F. above the rectal temperature. Winternitz (1881) seems to have been the first to measure

gastric temperature in normal subjects. He fastened a 4 cm. maximum thermometer to the tip of a rubber tube which was passed into the stomach. The experiments were designed only to ascertain the effects of external body chilling, and no numerical record of the gastric temperature is given. In 1917, Stengel and Hopkins seem to have been the first to record stomach temperatures with a thermocouple with a galvanometer and a potentiometer, the readings being taken in microvolts. The wires were run through an Einhorn tube. In 1925, Reis described a method for graphic registration of gastrointestinal temperature. He used an electrical resistance thermometer. The conductors were enclosed in an opaque tube, and its position in the intestinal tract could so be seen easily by use of the roentgenoscope. In Reis's work, there is no numerical record of gastric temperature. Kotschau and Roeloff (1927) used a thermocouple at the tip of a duodenal tube and were probably the first to supply a numerical record of gastric temperatures. Foged used a similar procedure, but extended the studies to include large numbers of normal subjects so that his findings are probably the most authentic. In Philadelphia, Hepburn, Eberhard, Ricketts and Rieger did some splendid work with gastric temperature recordings and made some determinations of associated gastric secretory changes. No roentgenologic records of gastric or intestinal motility were made. Our gastric temperature recordings agree essentially with the findings of these previous investigators. None of them, however, had carried out simultaneous determinations of gastric motor and secretory activity. While we have found some effect on gastric motility by hot and cold meals which resulted in varying roentgenologic intestinal patterns, we did not find an appreciable effect on gastric secretion, except for a short period following the ingestion of an ice-cold meal.

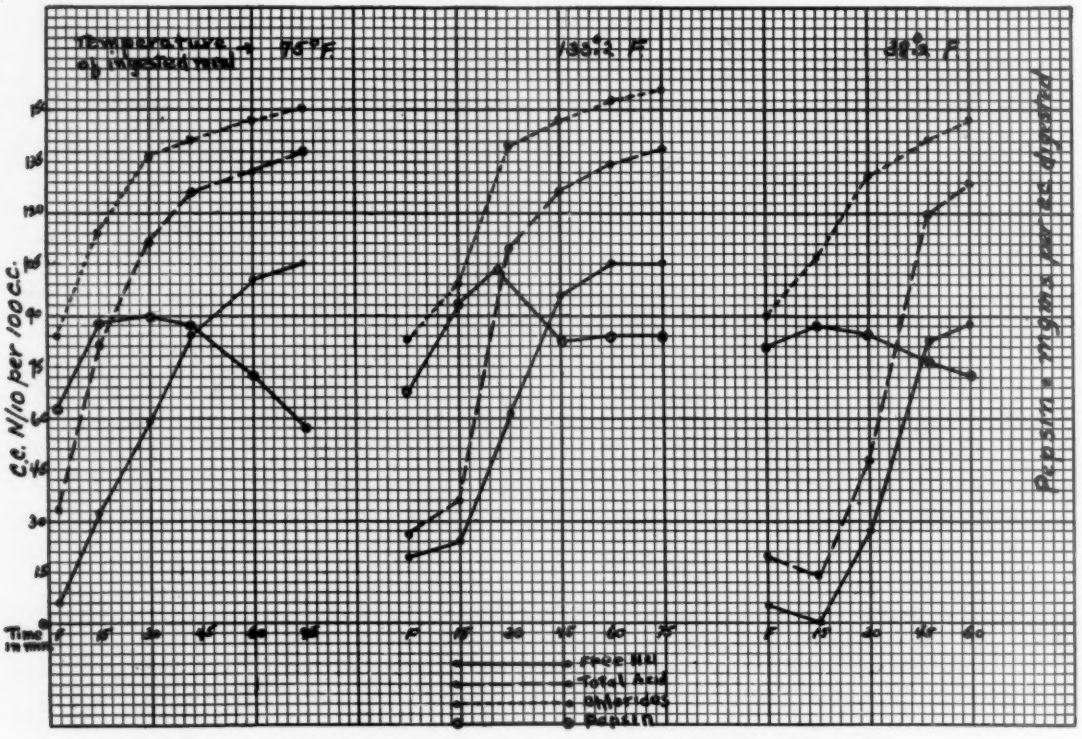

FIG. 3

SUMMARY

1. The normal gastric temperature as determined with sensitive thermocouples is approximately 99° F. and seldom varies more or less than 1° F. Its variation from subject to subject is as great as the mouth temperature.

2. An ice-cold liquid test meal chills the stomach 25–30° F. and it takes thirty-five to forty-five minutes before the gastric contents return to normal gastric temperature.

3. A hot liquid meal at 145–155° F. raises the gastric temperature immediately 6–10° F. which is overcome in fifteen to twenty minutes.

4. The colder the meal, the greater seems the rate of gastric evacuation.

5. Hot meals may empty more slowly than cold meals immediately after ingestion, but soon compensate by increased emptying after a short interval.

6. No appreciable effect has been noted on gastric secretion by very hot meals, but cold meals depress gastric secretion during the initial stages of digestion.

7. Summer diarrhea might be due partly to ice-cold drinks which effect too rapid gastric evacuation of gastric contents not effectively prepared for the intestines because of the depression in gastric secretions.

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DISCUSSION

Dr. T. Grier Miller, Philadelphia. A few days ago, before seeing Dr. Gershon-Cohen's paper and knowing little about the subject, I asked one of my associates, Dr. Hugh Montgomery, if he would not do for me an experiment on gastric temperature in man. He induced Dr. Abbott, of our staff and who is an expert at such things, to swallow a thermocouple and then eat some ice cream and drink a bottle of cold Coca-Cola. That produced a fall of Dr. Abbott's gastric temperature to 15° C. and it was thirty minutes before it reached normal again. Then he took a drink of hot water (50° C.), whereupon the temperature rose to 46° C. and dropped back to normal only after about twenty minutes.

These results, though surprising to me at the time, are in agreement with those of Dr. Gershon-Cohen and his associates. They are also in entire agreement with the data obtained by Stengel and Hopkins in our clinic more than twenty years ago. Stengel and Hopkins also studied the variation in temperature between the fundus and pylorus after hot and cold drinks, finding that it was always less affected in the pylorus.

Dr. Gershon-Cohen states that simultaneous investigations of the secretory and motor phenomena after hot and cold meals had not previously been made, which I believe to be correct, and he makes no reference to any earlier roentgen investigations of motility. I think, however, that mention should be made of the supplementary work of Weitz and Sterkel (1920) who observed a change from the "fish-hook" to the "steer-horn" type of stomach in subjects exposed to a cold environment; also to that of Sleeth and Van Liere (1937) who by the use of a barium meal found that external cold shortened the emptying time and external heat increased it. Kuenzel and Todd (1929), on the contrary, observed, under the fluoroscope, that external heat increased the activity and contraction of the stomach; also, that hot drinks had a similar effect.

In contrast to these observations Muller (1905), by administering fluids at varying temperatures and evacuating the stomach fifteen minutes later, concluded that the motility was greatest when the fluid approached body temperature. Basch and Mautner more recently (1930) found that greatest diuresis followed the intake of fluids of normal temperature. Their work, perhaps, in view of the present report, deserves repetition.

As to secretory changes, no reports after the ingestion of substances of varying temperatures have been found, but Yamana reported last year that ice packs applied to the abdominal

wall of rabbits and of man caused an increase in the quantity and acidity of the gastric contents, and Bogendorfer and Sell (1930) found a similar rise in secretory activity after cold applications but a diminution after heat. Fischer (1920), also, working with dogs having a Pavlov pouch, found that hot air baths reduced the quantity of secretion by 50 per cent.

Thus this literature, though not entirely consistent, suggests that cold increases the motor and secretory activity of the stomach, while heat has the opposite effect. The present work confirms that opinion as to the motor effects of cold substances in the stomach but otherwise indicates no striking changes after either cold or hot meals. I believe that the work reported here has been well done and that the results, tentatively at least, should be accepted.

DR. JOHN L. KANTOR, New York City. This work is clinically very helpful. It extends the previous observations which are a little paradoxical and somewhat confusing, and helps us understand the situation better.

As far as heat and cold are concerned, they work in the opposite direction according to whether the temperature is applied externally to the skin, or internally within the gut. Once that is understood, I think the rest is simple. In other words, as I understand it, it has heretofore been shown that heat applied externally to the skin relaxes spasm and depresses tone; heat applied internally within the lumen increases the tone of the viscus. Cold acts the opposite in both cases.

What has not hitherto been shown and therefore is the crux of this afternoon's presentation, is the behavior of the pyloric sphincter.

The question in my mind up to this very afternoon was, if heat applied internally increases tone, what happens to the sphincter? From what we have heard today, heat internally increases tone and at the same time seals the sphincter temporarily. This, however, is to be regarded as a benefit because of the improved gastric secretion and the increased time available for gastric digestion.

All this is in keeping with our clinical impression as to the harmfulness of cold drinks, which not only pass through quickly, carrying the cold into the bowels, but result in impaired juice content. The benefit of hot drinks is due to the opposite effect.

Finally, if one may bring this down to clinical usefulness, it would seem that we probably over-cold-feed some patients. The whole Sippy regimen is commonly administered on the ice-cold basis, and in my practice, the postoperative stomach at least is never treated on an ice-cold basis. I think heat is the thing that is needed, and I would therefore suggest that it may be also useful to heat some, if not all, the diets in the ulcer regimen.

DR. GERSHON-COHEN (closing). I should like to thank Dr. Miller and Dr. Kantor for their cordial résumé of this subject. We are particularly indebted to Dr. Miller for the fine tube that we now have at our disposal, which has opened up a tremendous new field of study in small intestinal conditions.

In the presentation of our paper, we studiously avoided mentioning anything about the effect of external chilling or external heating because that is a big problem on which there is already an extensive literature. The literature is scanty, however, in the field where the temperature of the meal itself has been studied.

We are carrying out a series of experiments with external heat and chilling in which the patients have showers before we give them their test meal, hot showers and cold showers, and immersion in water at different temperatures.

Essentially, all these experiments demonstrate the points that Dr. Kantor made and the probabilities are that when comparison is made between external and internal changes of temperature, the findings will be very much as Dr. Kantor very well outlined here this afternoon.

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VITAMIN B_1 IN IRRADIATION SICKNESS

PRELIMINARY REPORT

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INTENSIVE roentgen and radium therapy in the treatment of cancer and allied diseases is occasionally complicated by the development of dizziness, anorexia, nausea, and vomiting. If the symptoms are not marked, interruption of radiation therapy is not indicated, but persistent nausea and vomiting necessitate discontinuance of the treatment unless these symptoms can be controlled by some form of medication. This paper deals only with those cases which exhibited severe symptoms of irradiation sickness and then received oral or parenteral synthetic vitamin B_1 (thiamin chloride)* therapy. A total of 21 cases, summarized in tabular form, is presented in this report. In 7 of these cases, irradiation was directed to the breast area, 4 patients being treated by interstitial radium element needles. Of the remaining 14 cases, 12 received irradiation to the pelvis, 1 to the liver and spleen, and 1 to the left side of the neck.

A factor to be considered is the relative efficacy of the oral and parenteral preparations of vitamin B_1. In comparing the two methods of administration, the quantity of the drug used and the length of time necessary to produce complete relief of symptoms are important considerations. Marked anorexia, nausea, and dizziness can usually be controlled by 3,000 international units (I.U.) daily of the oral preparation, but where nausea, anorexia, and vomiting are present it is necessary to increase the dosage of the oral preparation to 6,000 I.U. or more daily for alleviation of the symptoms. In the majority of cases where the oral preparation of the drug is used, definite improvement does not occur before twenty-four to forty-eight hours. In contrast to this, the injected vitamin B_1 gives appreciable or complete relief within one to three hours. Cases XI and XII in Table 1 required 6,000 I.U. of the oral preparation daily to control the ill effects of irradiation. In order to note the relative amount required, the medication in both these cases was changed to the hypodermic form, using one-half the oral dose, and complete freedom from symptoms was maintained with the daily use of 3,000 I.U. of the hypodermic preparation.

Sponheimer[3] reports only slight improvement in symptoms as a result of oral administration of vitamin B_1, but states that complete relief was obtained by the use of the parenteral therapy. Martin and Moursund[2] report favorable results following administration of the oral preparation, and they resort to intramuscular injection only when vomiting occurs. These authors have observed that where serious complications, such as partial bowel obstruction, are present, vitamin B_1 therapy is ineffective. We have observed one such case, Case X in Table 1, which did not show definite response to vitamin B_1 therapy. Autopsy in this case disclosed the presence of a partial bowel obstruction in the region of the cecum.

We find that daily injections of 3,000 I.U. will, in the majority of cases, give rapid and complete relief. Infrequently, a recurrence of symptoms requires a temporary or permanent increase in the dosage. One patient receiving roentgen therapy to the left side of the neck required a temporary increase to 4,500 I.U. daily by hypodermic injection for control of recurrent nausea. In only a small percentage of cases

* Synthetic vitamin B_1 (thiamin chloride) used to carry out this clinical survey was supplied as Betaxin by courtesy of the Medical Research Department of the Winthrop Chemical Company, and as Betalin S by courtesy of Eli Lilly and Company.

TABLE I

SUMMARY OF 21 CASES OF IRRADIATION SICKNESS RECEIVING VITAMIN B_1 THERAPY

Case	Age and Sex	Diagnosis	Roentgen Therapy	Radium Therapy	Other Therapy	Symptoms	Dosage of Vitamin B_1	Results
I	33 F	Carcinoma simplex, right breast	None	Interstitial radium element needles to breast; 102 mg. radium for 19,227 mg-hr.	None	Anorexia, nausea, and vomiting after 3,000 mg-hr. of irradiation. Recurrence of nausea 24 hours after stopping the medication	Injection of 3,000 I.U. daily for 8 days. Medication stopped on day of removal of radium. Injection of 3,000 I.U. daily for 3 days for recurrent nausea	Rapid control of all symptoms during periods of B_1 administration
II	42 F	Carcinoma simplex, left breast	None	Interstitial radium element needles to breast; 103 mg. radium for 26,471 mg-hr.	None	Anorexia, nausea, and vomiting after 4,000 mg-hr. of irradiation. Recurrence of nausea 40 hours after stopping the medication	Injection of 3,000 I.U. daily for 7 days. Medication stopped after 17,000 mg-hr. Injection of 1,500 I.U. daily for 2 days, then 450 I.U. orally for 5 days	Rapid control of all symptoms during periods of B_1 administration
III	30 F	Carcinoma simplex, left breast	None	Interstitial radium element needles to breast; 109 mg. radium for 23,896 mg-hr.	None	Anorexia, nausea, and vomiting after 4,000 mg-hr. of irradiation	Injection of 3,000 I.U. daily for 2 days. Dosage increased to 6,000 I.U. daily for 3 days. Dosage increased to 10,000 I.U. daily for 4 days	Definite improvement with dosage of 3,000 and 6,000 I.U. daily. Absence of all symptoms with 10,000 I.U. daily
IV	67 F	Carcinoma simplex, left breast, postoperative. Carcinoma simplex, right breast	One port right breast and each axilla for 1,600 r to each port. Two ports pituitary for 650 r to each port	None	None	Anorexia, nausea, and dizziness 15 days after institution of therapy	Injection of 3,000 I.U. daily for 2 days. Dosage increased to 6,000 I.U. daily for 3 days	Complete relief with daily dosage of 6,000 I.U.
V	67 F	Carcinoma simplex, left breast, postoperative. Carcinoma simplex, right breast	Cases IV and V are same patient. See therapy above. Radium therapy 13 days after completion of roentgen therapy	Interstitial radium element needles to right breast; 95 mg. radium for 16,072.5 mg-hr.	None	Nausea and vomiting after 2,400 mg-hr. of irradiation. Reduced dosage of B_1 followed by recurrence of nausea	Injection of 6,000 I.U. daily for 2 days. Dosage reduced to 3,000 I.U. daily for 3 days. Dosage increased to 6,000 I.U. daily for 3 days	Daily dose of 6,000 I.U. necessary for complete relief of symptoms
VI	54 F	Carcinoma simplex, right breast	Three ports right breast for 2,000 r to each port	None	None	Anorexia, nausea, and dizziness 15 days after institution of therapy	Injection of 3,000 I.U. daily for 6 days. Dosage increased to 6,000 I.U. daily for 11 days	Symptoms alleviated with 3,000 I.U. daily. Absence of all symptoms with 6,000 I.U. daily
VII	58 F	Inflammatory carcinoma, left breast	Two ports left breast for 1,850 r to each port. One port left supraclavicular region and one port left axilla for 1,775 r to each port	None	None	Anorexia, nausea, and vomiting 24 days after institution of therapy	Injection of 3,000 I.U. daily for 8 days	Rapid control of all symptoms

VIII	52 F	Hodgkin's disease	Directly to liver and obliquely to spleen for 8,000 r to each port. Both supraclavicular areas, left axilla and right groin for 320 r to each of four ports	None	Transfusions	Anorexia, nausea, and weakness 2 days after institution of therapy. Recurrence of nausea with second series of roentgen treatments	Injection of 3,000 I.U. daily for 13 days; 450 I.U. orally for 32 days between the two series of roentgen treatments. Injection of 3,000 I.U. daily for 18 days	Complete control of all symptoms during periods of B_1 administration
IX	48 F	Basal cell carcinoma of cervix. Epidermoid carcinoma in subcutaneous tissues of neck	One port to left neck for 2,000 r. Two ports pituitary for 650 r to each port	None	None	Anorexia and nausea 4 days after institution of therapy. Recurrence of nausea 13 days after institution of therapy	Injection of 3,000 I.U. daily for 8 days. Injection of 4,500 I.U. daily for 5 days. Injection of 3,000 I.U. daily for 12 days	Rapid control of all symptoms. Recurrent nausea treated satisfactorily with temporary increase in dosage. Uncontrollable nausea with previous roentgen therapy to pelvis
X	43 F	Carcinoma of cervix	Three anterior and three posterior ports to pelvis for 160 r to each port; 19 days later same ports used for 320 r to anterior and 240 r to posterior ports	None	Intravenous glucose. Liver extract. Transfusions	Persistent nausea and anorexia and occasional vomiting prior to roentgen therapy. Roentgen therapy aggravated all symptoms	Injections of 1,500 I.U. daily for 7 days, then stopped for 2 days. Daily injection of 1,500 I.U. resumed and given for 13 days	Some relief of nausea during periods of B_1 administration. Invasion of cecum with partial bowel obstruction revealed at autopsy
XI	55 F	Papillary squamous carcinoma of cervix	Three anterior and three posterior ports to pelvis for 2,150 r to each port	Intrauterine and intravaginal radium for 9,216.9 mg-hr. Radium therapy started 3 days after completion of roentgen treatments	None	Anorexia, nausea, and vomiting 16 days after institution of roentgen therapy. Radium therapy produced no symptoms	3,000 I.U. orally for 2 days; 6,000 I.U. orally for 2 days. Injection of 3,000 I.U. daily for 16 days	6,000 I.U. orally necessary to control symptoms. Complete relief with daily injection of 3,000 I.U.
XII	77 F	Squamous carcinoma of cervix	Three anterior and three posterior ports to pelvis for 1,600 r to each port	None	None	Extreme anorexia and nausea 3 days after institution of roentgen therapy	3,000 I.U. orally for 2 days; 4,500 I.U. orally for 1 day; 6,000 I.U. orally for 4 days. Injection of 6,000 I.U. daily for 2 days. Injection of 3,000 I.U. daily for 14 days	6,000 I.U. orally necessary to control symptoms. Complete relief with injection of 3,000 I.U. daily
XIII	74 F	Squamous carcinoma of cervix	Three anterior and three posterior ports to pelvis for 2,000 r to each port	Intrauterine and intravaginal radium for 9,350.4 mg-hr. Radium therapy started 10 days after completion of roentgen treatments	None	Anorexia, nausea, and dizziness 3 days after institution of roentgen therapy. Radium therapy produced no symptoms	Injection of 1,500 I.U. daily for 5 days. Injection of 3,000 I.U. daily for 20 days	1,500 I.U. daily did not give complete relief. All symptoms controlled by daily injection of 3,000 I.U.
XIV	27 F	Anaplastic epidermoid carcinoma of cervix	Three anterior and three posterior ports to pelvis for 2,200 r to each port	Intrauterine and intravaginal radium for 7,702.4 mg-hr. Radium therapy started 1 day after completion of roentgen treatments	None	Anorexia and nausea 3 days after institution of roentgen therapy. Radium therapy produced no symptoms	Injection of 3,000 I.U. daily for 20 days	Rapid control of all symptoms

TABLE I—(*Continued*)

Case	Age and Sex	Diagnosis	Roentgen Therapy	Radium Therapy	Other Therapy	Symptoms	Dosage of Vitamin B_1	Results
XV	53 F	Squamous carcinoma of cervix	Two anterior and two posterior ports to pelvis for 1,600 r to each port	None	None	Nausea, dizziness, and vomiting 12 days after institution of roentgen therapy	Injection of 3,000 I.U. daily for 10 days	Rapid control of all symptoms
XVI	61 F	Squamous carcinoma of cervix	Three anterior ports to pelvis for 2,000 r to each port	None	None	Nausea and vomiting 2 days after institution of roentgen therapy. Recurrence of symptoms 30 hours after stopping medication	Injection of 3,000 I.U. daily for 10 days. With recurrence of symptoms, injection of 3,000 I.U. daily for 9 days	Complete control of all symptoms during periods of B_1 administration
XVII	39 F	Anaplastic carcinoma of cervix	Three anterior and three posterior ports to pelvis for 2,200 r to each port	Intravaginal radium for 2,160 mg-hr. to control bleeding	Transfusions	Nausea and vomiting 18 days after institution of roentgen therapy. Recurrence of symptoms with reduced dosage of B_1	Injection of 3,000 I.U. daily for 2 days. Injection of 6,000 I.U. daily for 5 days. Injection of 3,000 I.U. 1 day. Injection of 6,000 I.U. daily for 4 days	Injection of 6,000 I.U. necessary for effective control of all symptoms
XVIII	42 F	Multiple papillomata of bladder	Three anterior ports to pelvis for 2,400 r to each port, and three posterior ports to pelvis for 2,200 r to each port	None	None	Anorexia, nausea, and dizziness 22 days after institution of roentgen therapy	Injection of 3,000 I.U. daily for 3 days	Rapid control of all symptoms
XIX	32 F	Anaplastic carcinoma of cervix	Three anterior and three posterior ports to pelvis for 2,200 r to each port	Intrauterine and intravaginal radium for 9,986.6 mg-hr.	None	Roentgen therapy produced no symptoms. Anorexia and nausea after 5,000 mg-hr. of irradiation	3,000 I.U. orally for 5 days	Complete control of all symptoms within 36 hours
XX	42 F	Inflammatory carcinoma, right breast	Ovarian castration with two anterior and two posterior ports for 960 r to each port	None	None	Anorexia, nausea, and dizziness on day of first roentgen treatment	3,000 I.U. orally for 2 days; 6,000 I.U. orally for 13 days	6,000 I.U. orally necessary to control symptoms
XXI	36 F	Carcinoma simplex, right breast	Ovarian castration with two anterior ports for 960 r to each port. Two ports to pituitary for 650 r to each port	None	None	Anorexia and nausea 7 days after institution of roentgen therapy	Injection of 6,000 I.U. on alternate days for 3 doses	Alleviation of symptoms, but not so satisfactory as when medication given daily. Uncontrollable nausea with previous roentgen therapy to right breast

is it necessary to increase the daily injections to 6,000 I.U. or more. One patient, treated by application of interstitial radium element needles to the left breast area, required daily injections of 10,000 I.U. to eliminate nausea and vomiting. The results obtained with the hypodermic preparation are definitely superior to those following use of the oral preparation. We have therefore discontinued the oral therapy except for purposes of study.

The treatment of out-patients presents a different problem in that those patients who develop irradiation sickness cannot be satisfactorily relieved of their symptoms simply by the oral administration of large doses of vitamin B_1. Many such cases feel so ill that it is difficult to retain their confidence and cooperation, with the result that they fail to continue the medication as prescribed and occasionally refuse to follow the course of radiation therapy as outlined. This undesirable factor can be overcome by requiring the patient to return to the hospital or to his physician for daily injections of vitamin B_1. Sometimes it is necessary to hospitalize these patients in order to secure their cooperation and treat them effectively. We have treated out-patients receiving irradiation three times each week by giving them an injection of vitamin B_1 on the days when they received roentgen therapy. This particular usage of the drug did not prove effective, and symptoms were not completely controlled unless the patient was given daily doses of vitamin B_1. It is therefore apparent that smaller daily doses are more effective in the control of irradiation sickness than are massive doses given on alternate days.

A number of in-patients who developed irradiation sickness were effectively relieved by vitamin B_1 therapy, which was then temporarily discontinued in order to note recurrence of symptoms and the time factor in their reappearance. In all such cases there was a return of the nausea and anorexia within twenty-four to forty-eight hours after the medication was stopped. This finding further emphasizes the value of the daily administration of vitamin B_1 in preference to larger doses of the drug given every other day.

Martin and Moursund[2] have called attention to the fact that serious symptoms are produced only when some portion of the intestinal tract or the parotid gland is included in the area under treatment. Our findings differ somewhat in that we have not found that radiation therapy to the parotid region is apt to produce severe symptoms. We have, on the contrary, observed less incidence of irradiation sickness in cases where therapy was directed to the parotid region than in those receiving radiation therapy to other portions of the body. A number of cases of irradiation sickness have been observed among patients receiving massive doses of radiation in the form of interstitial radium element needles for cancer of the breast. Four of the cases treated by interstitial radium element needles are summarized in Table 1.

We have had one patient, Case XIX in Table 1, symptomless during roentgen therapy to the pelvis, who developed marked anorexia and nausea following intrauterine and intravaginal application of radium. This case demonstrates irradiation sickness following protracted irradiation, and the symptoms were here effectively controlled with 3,000 I.U. daily of the oral preparation. Of all the cases which suffered ill effects from intensive roentgen therapy to the pelvis, none has shown a recurrence of symptoms during the following intrauterine and intravaginal application of radium.

In those cases which are to receive intensive roentgen therapy, Martin and Moursund[2] begin the use of vitamin B_1 orally two days preceding the first radiation treatment. We do not feel that such general prophylactic use of vitamin B_1 is indicated, since the symptoms are readily controlled by use of the hypodermic preparation, and since patients who develop irradiation sickness are definitely in the minority in comparison to the number of cases showing no ill effects from roentgen or radium

therapy. However, where interstitial radium element needles are used for cancer of the breast, there is as a rule an early and severe onset of anorexia, nausea, and vomiting, and the prophylactic use of vitamin B_1 may therefore be justified in these cases.

Further investigation of irradiation sickness, paralleled by daily or twice daily estimations of vitamin B_1 content in the blood serum, beginning two days before institution of radiation therapy, might be of scientific interest in the indication of a possible direct relationship between the actual level of vitamin B_1 and the onset of irradiation sickness.

CONCLUSIONS

1. Irradiation sickness is controlled rapidly and effectively by the administration of vitamin B_1 in large doses.

2. The hypodermic preparation of vitamin B_1 gives more satisfactory results, and the amount required is usually only half that necessary when the drug is given orally.

3. Vitamin B_1 therapy is most effective when daily doses are administered.

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EFFECTS OF ROENTGEN IRRADIATION UPON THE BLOOD VESSELS OF REPAIR TISSUE AND THE BROWN-PEARCE RABBIT EPITHELIOMA*†

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THE PURPOSE of this study is to investigate the *in vivo* changes produced by a large single massive dose of roentgen radiation (10,000 r) upon the blood vessels, especially the capillaries of control and tumor sites. The Brown-Pearce rabbit epithelioma was transplanted in a modified Clark chamber[6,14,28] in the rabbit's ear in order that the sequence of these changes might be followed under suitable magnification.[15] Changes occurring in the smaller blood vessels immediately after the application of 10,000 r were striking and unexpected even with this large dosage. The grossly observable erythema appeared upon the fifth day, remained for the usual time, and did not seem atypical. While the magnitude of the changes noted in the finer structures is probably dependent to a great extent upon the dosage used, the sequence of events in the blood vessel damage is probably representative of the changes which occur with lesser dosage. Since these changes are of great interest to those engaged in tumor therapy they are reported in some detail.

Many observations have been made upon fixed tissues.[1,17,19,21,24,32] There are few data available concerning the effect of radiation upon the living, intact blood vessels in warm-blooded animals or human beings. A few observations upon the smaller vessels of the human skin have been described by David and Gabriel[8,11] and Siedamgrotzky,[29] who reported an increase in the number of end loops in the small vessels of the human skin during the erythema and changes in contractility of the larger vessels. Perfusion experiments with rabbit's ears by Lazarew and Lazarewa[18] suggested that a hyperemia was present during the erythema stage. Most of the studies have been concerned with the grossly visible, erythema reaction. This visible reaction, with its peculiar time sequence described by Miescher[22] and Reisner[26] is little understood.

In the past two decades there has been a good deal of discussion concerning the effects of roentgen irradiation upon the blood vessels in and around the tumor mass. In 1904 Baermann and Linser[2] suggested that any destruction of irradiated tumors must depend upon *primary* vascular lesions and thus drew attention to degenerative changes in the intima of blood vessels accompanied by thrombosis. Bowen[4] in 1908 found that complete obliteration of the blood supply to the tumor by surgical means resulted in mortification or gangrene, separation, and cure; while in 1936 Chambers and Scott,[5] as a result of a series of experiments started in 1932, declared that *temporary* obliteration of the blood supply (not long enough to damage the blood vessels sufficiently to prevent a return or re-establishment of circulation) seemed to cause tumor regression. Woglom,[33] in his 1922–1924 survey of the cancer problem, came to the conclusion that interference with blood supply was a factor in tumor regression. Ewing[10] in his 1925 Caldwell Lecture stated that "a large part of the destructive effect of roentgen rays upon tumors . . . is caused by interference with the blood and lymph circulation. There have been described rupture of capillaries, hemorrhage, thrombosis, com-

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pression of capillaries by exuded lymphocytes and plasma cells and growth of new connective tissue, swelling of all coats of large arteries, late arterial sclerosis, and the anemic condition of the radiation cicatrix." According to Cramer,[7] all effects following irradiation are related to vascular stimulation and vascular degeneration, whereas Pullinger[25] declared that the causes of cell death in irradiated human tissue are due to an interruption of the blood supply through hemorrhage followed by organization, scarring, and pressure atrophy. Pack[23] called attention to the fact that "in the case of many individual tumors the fundamental nature of the tissue of origin outweighs all other considerations when an attempt is made to estimate the radiosensitivity. Thus the primitive blood-forming tissues predetermine the radiosensitivity of tumors developing from their lymphoid, myeloid, and vascular derivatives." Pohle[24] and others[9] have had similar points of view.

Michels' 1935–1936 papers[21] review the theories concerning capillary contractility and point out that from his experiments with a single massive dose of 400 r over the rabbit's abdomen the capillary endothelium of the mesentery seems to be relatively sensitive to irradiation since involution and sloughing of the endothelial cells may occur with this dosage. This is accompanied by the loss of function of some capillaries. (See also refs. 16 and 32.) In 1936 Warren[31] reviewed the work done up to that time on the physiological effects of roentgen irradiation upon normal body tissues and stated that the blood vessels seemed to be among the more radioresistant organs of the body.

It may be seen from the above brief summary that while the rôle of irradiation effects upon the blood vessels of a tumor is an important one, the sequence of events *in vivo* after irradiation is not known nor has the character of the changes produced been identified with any certainty.[31] It is possible that the simple rabbit ear chamber[15] may introduce certain modifications in the tumor vessels, yet the vascular response to growth of the tumor transplant is so consistent as to make it seem an ideal subject for observation of the changes in the vessels in control and tumor tissues brought about by large single massive doses of radiation. Enough observations have been made upon the vascular pattern in control sites and tumor sites (150 animals) to warrant the statement that the observed changes are due to the radiation and do not depend upon any fortuitous circumstances.

APPARATUS AND METHODS

In previous experience with tumor transplants in the ear chambers of the rabbit in this laboratory,[15] it was obvious that many improvements had to be made in the lighting and arrangement of photographic equipment before photographic observation of tissues under the "window" could be accomplished with ease and accuracy. Considerable difficulty was also encountered in preparing a window of suitable shallowness which not only would allow good observation of blood vessel growth under high magnification but would also allow the tumor to grow to an appreciable physical size so that a pure "tumor vascularization" could be obtained in this acute type of experiment.

In the interests of compactness and ease in making observations through the window in the rabbit's ear, the conventional design for a photomicrographic apparatus[12,13,20,27,30] was abandoned in favor of a completely vertical arrangement. The source of light, condensing system, microscope and camera were centered along one axis and fixed accurately in position with the plane of the plate or film, the latter being parallel to the microscope stage holding the rabbit's ear (Fig. 1). The microscope and camera were physically separated to avoid the transmission of vibrations from the blower or the camera motor.

The focusing device used with the motion picture camera is different in that, unlike most of the current viewing set-ups, it does not employ a beam-slitting device and thus cause the loss of part of the light. The camera lens and the eyepiece of the microscope are both removed to avoid reflecting surfaces. By means of a lens-

mirror system the image is focused directly upon the film when the camera is in operation and on the shutter (which is painted white) when the camera is still. This enables the operator to focus carefully before starting the camera and then to "panoram" with ease, and to refocus for any slight variation in depth throughout the rabbit ear chamber thus maintaining the critical focus on the film. Changes in the light are easily noted and adjustments in exposure made as necessary.

Since tungsten filament lamps of high wattage should not be burned horizontally, a compromise had to be made with regard to the light source. Therefore, the lamp socket was mounted so that the tungsten filaments were at a 45° angle with relation to the condensing system of the apparatus. This gave excellent illumination with maximum life of the bulb while eliminating one reflecting surface—the substage mirror of the microscope. A blower was used to cool the lamp. Neutral density filters (0.3, 0.6, 0.9) were used alone or in combination as protection for the eyes of the experimenter while locating fields in the operated area. Color filters were not used in the color photography of the thinner windows. A simple exposure meter was employed, the construction details of which are described elsewhere.[3]

A flat-topped animal board was constructed so that when the animal was placed on it comfortably in the prone position,[6,16] the ears were in a straight line level with the mechanical stage of the microscope, and complete mobility of the rabbit in a 150° radius with regard to the microscope was assured. By working at night in a quiet room with a trained rabbit and by avoiding fatigue of the rabbit, many psychic and other factors which might influence the reaction of the blood vessels were minimized. Patient and careful training of the rabbit is obviously essential to success with photography and observations under magnification.

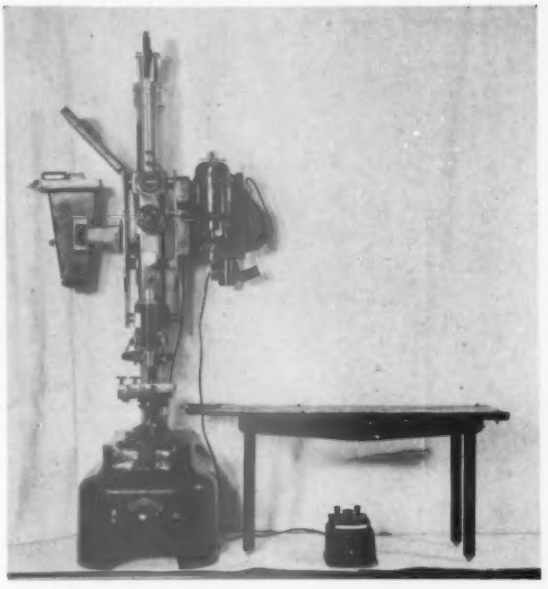

Fig. 1. This shows the microscope mounted on the heavy cast-iron base. The cameras are mounted on an old roentgen tube stand which contains a counterweight. The camera for still photographs is mounted on the left with the mirror at an angle above the ground glass to simplify focusing. The modified 16 mm. camera and driving motor are seen at the right. The camera lens is replaced by a constant viewing device containing a mirror and a built-in photocell. The wire extends from this to the galvanometer on the table. The same leads may be connected with the photocell built into the still camera, shown on the left. Either camera may be swung into place with ease. The special rabbit board is shown at the right of the base of the apparatus.

PREPARATION OF WINDOW

The preparation of the window chamber is essentially the same as that previously reported[15] except for certain improvements. A $\frac{3}{8}$ inch nickel gromet and washer were inserted in the ear about 1.5 cm. from the tip and an aluminum templet used to establish the exact distance (1 cm.) from the gromet to the upper incision of the operated area. The gromet fits over a post soldered to the mechanical stage, thus fixing the position of the chamber under the microscope. Where stability is desired during examination of the operated field, this method of immobolization is simpler for this "acute experiment" than others requiring the exertion of pressure upon the ear, since normal circulation is not impaired.

The 1 sq. cm. skin area to be operated upon was then delineated and a scalpel nick made in the skin in one corner, and the skin stripped or rolled off with as little traumatization of blood vessels as possible (suggested by Dr. G. O'Hara). Stripping, rather than sharp dissection of the skin from both sides of the ear over this 1 sq. cm. area leaves intact the perichondrium with its blood vessels. Subsequent

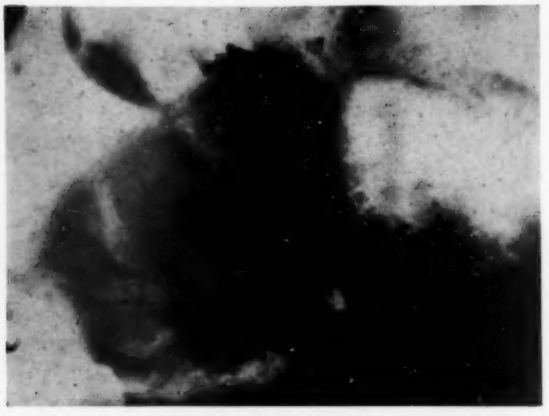

FIG. 2. One day after operation. The dark areas outside of the central dense tumor mass are due to masses of red blood cells (60×).

hemorrhage into the chamber, which was previously a handicap, was thus minimized.

Due to the short duration of this type of experiment a simple window was employed rather than the more complicated one necessary for the type of studies engaged in by Clark *et al.* Rectangles of cleared dental x-ray film 2¼×1½ inches, colored filter material (Blue No. 80), various grades of Kodapak (12×18 inch sheets), and cellulose acetate (20×50 inch sheets—thickness 0.0075 inch) were tried. The last was found most satisfactory for work requiring ordinary magnifications. For oil immersion examination, cellulose acetate (20×50 inch sheets—thickness 0.02 inch) with the center replaced by cover glasses fastened with collodion were used. The "window" was sterilized in alcohol before being used.

The sterile rectangular piece of cellulose acetate sheet to be used as a "window" was placed on either side of the ear overlapping the operated site and sewn in place, care being taken in sewing to avoid all visible blood vessels. The windows were then cut *in situ* so as to be roughly elliptical, thus avoiding trauma due to sharp corners. The area from sutures to window edge was covered above and below with collodion to provide an air-tight and fluid-tight seal.

Just before the last few stitches were made in the window of the rabbit's *right* ear, a very small piece of fresh, actively growing Brown-Pearce rabbit epithelioma was implanted, i.e., placed on the tissue of the "stripped" area just beneath the window. The left ear was treated in exactly the same manner except for the tumor implant (which is omitted) since this ear was to be used as a control.

At the proper time after operation (ten to fifteen days) a dosage of 10,000 r including back-scattering was administered through a 5 cm. portal to the chamber areas of the right and left ears by means of a Machlett water-cooled tube operated with no filter, full-wave rectification, 90 kv. (peak) (sphere gap), 17 ma. for 26.6 minutes at a target-mid-ear distance of 27.6 cm. For measurement, the middle of the ionization chamber was placed in air at the usual mid-ear position on the animal board at 27.6 cm. from the center of the target. The ionization chamber of the calibrated Victoreen r-meter was 1.2 cm. in diameter and the average thickness of the rabbit's ear in the operated area was 0.5 cm. including both cellulose acetate "windows." At the termination of the experiments the upper two-thirds of the ears, including the window area, were removed under general anesthesia and the specimens prepared (hematoxylin and eosin stain) for microscopic examination.

EXPERIMENTAL DATA

The following is a description of a typical experiment. Except for minor variations in the time relations, the results were identical for all 7 rabbits upon whom the roentgen irradiation was practiced. The stages of growth before irradiation are almost similar to the studies previously reported,[15] yet there are some additional details which differ because of the cham-

FIG. 3. Two days after operation. Punctate clumping on the left, near the tumor mass; a few vessels are seen elsewhere. A good many of the free red blood cells have disappeared (50×).

ber dimensions and the technique employed so that these are described:

Rabbit No. 95

(White, young, adult, male rabbit from tumor susceptible stock)
Weight=6 pounds.

2-1-38 16 days before operation	Training period begun. Animal placed on board twice daily.
2-14-38 2 days before operation	Hair removed from rabbit's ears in preparation for operation. Slight irritation of skin of both ears noticed.
2-15-38 1 day before operation	Practically no irritation or erythema of skin of ears noticed.
2-16-38 *Operation* Window sewed in place	Brown-Pearce rabbit epithelioma fragment placed under the "window" in the right ear. *No* Brown-Pearce rabbit epithelioma placed under the left (control ear).
2-17-38 1 day postoperative	See Figure 2. *Tumor Implant:* Some blood vessels show traumatic aneurysms. No neovascular response as yet. Clumps of red blood cells are spread throughout the chamber without clotting. *Control Chamber:* Some instances of traumatic aneurysms noted. No neovascular response. Some clumps of red blood cells but no clotting.

FIG. 4. Three days after operation. Note the vessels growing in from the sides especially on the left. The clumps of red blood cells are more sharply localized. A few are new (50×).

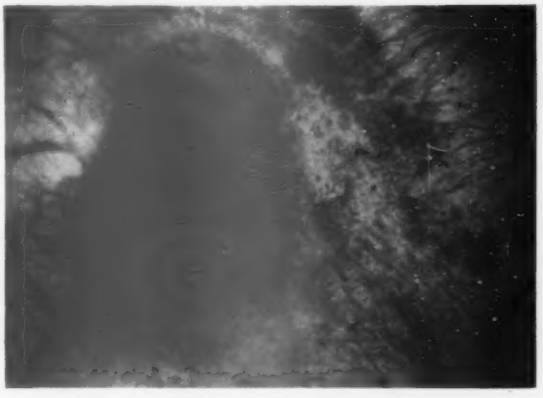

FIG. 5. Five days after operation. Well developed vascular supply and actively growing tumor spreading most rapidly toward the right. The left border of the tumor is growing vertically (increasing thickness). Secondary punctate hemorrhages (probably the result of trauma) are noted on the right (50×).

2-18-38 Second day	See Figure 3. *Tumor Implant:* Eddy currents noted in the plasma and red blood cells suspension in vicinity of tumor implant. No change in size of tumor particle. No other changes noted except punctate clumping of red blood cells. *Control Chamber:* No changes noted.
2-19-38 Third day	See Figure 4. *Tumor Implant:* Numerous new small compact hemorrhagic areas seen surrounding tumor implant. No other changes visible. *Control Chamber:* Diffuse clumps of red blood cells in the plasma still noticeable. No other changes noted.
2-20-38 Fourth day	*Tumor Implant:* Original hemorrhagic areas seem to be in the process of resorption. "End loop" formation noted as part of vascular pattern of new small vessels growing in the small compact clumps of red blood cells—toward the tumor and from the periphery of the operated area. *Control Chamber:* No changes noted.

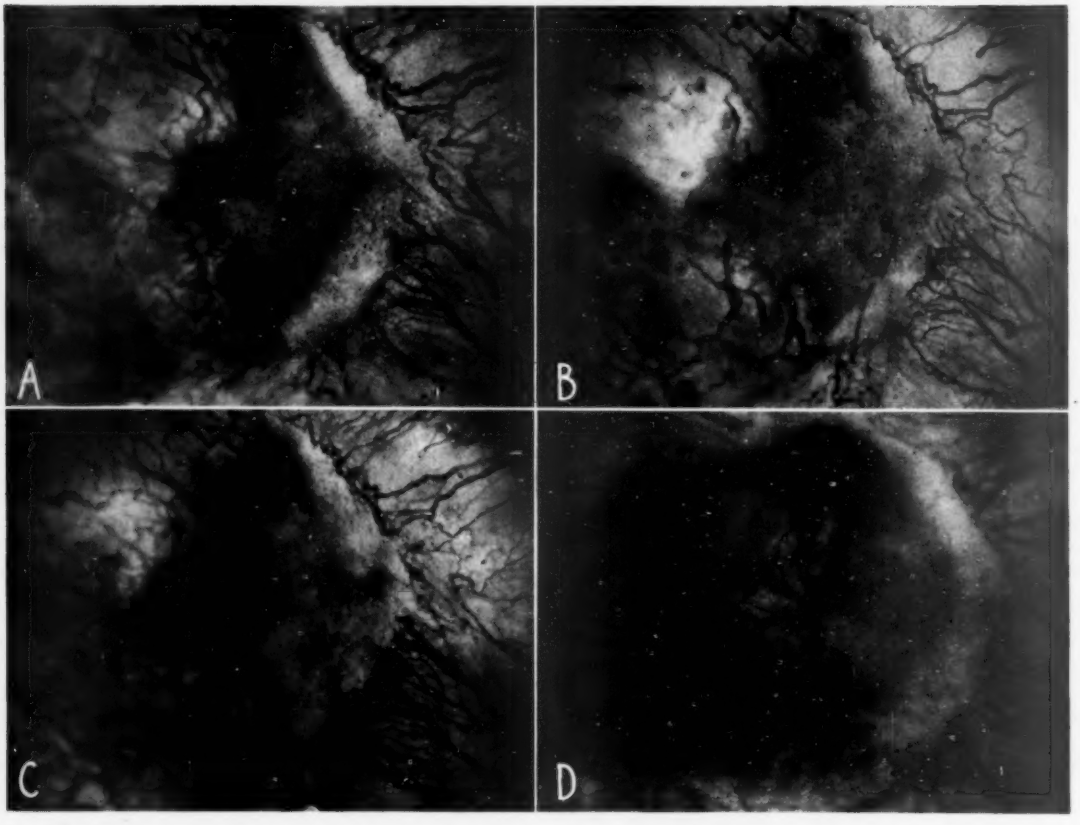

FIG. 6. Succession of changes over eight, nine, ten and twelve days after transplantation. The details of any plane are obscured by the thickness of the tumor growth. The centrifugal growth of the vessels is well shown at eight days, *A*. The great number of large and small vessels and the large amount of tumor slowly obscure the field (twelfth day, *D*). The roughly oval central dense mass represents the remnant of the original transplant which is well vascularized although the vessels are empty (50×).

2-21-38
Fifth day

Figure 5.

Tumor Implant: Original hemorrhagic areas seem to be almost totally resorbed. Slight increase in size of tumor fragment. A few new small hemorrhagic areas noted near growing edge of tumor fragment. A rich, seemingly haphazard growth of blood vessels from periphery of operated area is seen growing toward tumor fragment.

Control Chamber: Incipient vascularization evident at edges of operated area.

2-22-38
Sixth day

Tumor Implant: Evidence of increased vascularization noticeable. Some sinusoid formation seen.

Control Chamber: Slow growth of blood vessels centrad from periphery of operated control area.

2-23-38
Seventh day

Tumor Implant: Second series of new vessel loops noted with blood vessels growing into tumor mass. There blood vessels seem to be growing *in* and the tumor edge seems to be growing *out*. Growing edge of tumor fragment partially surrounded by punctate hemorrhagic areas.

Control Chamber: Continued slow growth of blood vessels centrad from periphery of operated area. Blood vessels now one-third of distance from periphery to center of operated area.

2-24-38
Eighth day

See Figure 6.

Tumor Implant: Tumor fragment increasing in size and changing

from pear-shape to an elliptical one. Some of the former small new vessels have increased in size and many of the smaller vessels have entirely disappeared.

Control Chamber: Little change noted.

2-25-38
Ninth day

See Figure 6.

Tumor Implant: Some slight resorption of punctate hemorrhages. Steady but rather slow growth of blood vessels and tumor edge.

Control Chamber: Slow growth of blood vessels centrad, now almost one-half of distance to center of chamber.

2-26-38
Tenth day

See Figure 6.

Tumor Implant: Increase in size and decrease in number of filled blood vessels going to and from tumor fragment continues.

Control Chamber: Little change noted.

2-27-38
Eleventh day

Tumor Implant: Vascular pattern about tumor seems fairly well settled. Little change from previous day as to size or arrangement of blood vessels evident. Hemorrhagic areas clearing slowly. Chamber now nearly filled with tumor mass. Tumor almost a spheroid and expansion and vascularization almost (but not quite) at a standstill.

Control Chamber: Little change noted.

2-28-38
Twelfth day

See Figure 6.

Tumor Implant: Rupture (? trauma) of endothelial tubes of new growing capillaries with hemorrhage without clotting noted. Tumor and blood vessels growing slowly but steadily with little change in vascular pattern now as compared with active proliferation, alteration, and disappearance of some of the vessels seen during the first ten days of tumor growth.

Control Chamber: Little change noted except continued slow growth of blood vessels centrad from the periphery of the operated area and the gradual resorption of punctate hemorrhagic areas.

3-1-38
Thirteenth day

Tumor Implant: Large, thin-walled blood vessels (obviously capillaries of a sinusoidal type) make readily visible various phenomena such as reversal of flow, "plasma skimming" (a process which brings about a reduction in the number of red blood cells and may even cause their entire disappearance from a certain capillary field), true "stasis" with consequent packing of red blood cells in capillaries, passive diapedesis, and active penetration of endothelial walls by wandering white cells. The chamber is almost ready for irradiation.

Control Chamber: Little change noted.

3-2-38
Fourteenth day

Tumor Implant: All traces of hemorrhage originally seen in tumor chamber have disappeared and the punctate secondary hemorrhagic areas are scarcely noticeable. Tumor has been changing by degrees from an elliptical to a spherical shape but the vascular pattern has remained essentially the same for the past four days (Fig. 7 *A*).

Control Chamber: The blood vessels have continued to grow slowly from the periphery of the operated area toward the center and have now almost filled the area (Fig. 7 *B*).

3-3-38
Irradiation

Tumor Implant: Irradiated tumor with 10,000 r without trauma. One-half hour after irradiation was completed (Fig. 7 *D* and *G*), a slight reddish haze was noted under various magnifications. It was impossible to tell whether this was due to a diffuse spread of the red blood corpuscles throughout the area or to hemolysis. This color change was not due to any change in the volume of blood present in the vessels (which continued unchanged but seemed to be due to extravascular change).

Control Chamber: A haze similar to that in tumor implant chamber also noted in control ear which also received 10,000 r as described in the *Method.*

3-4-38 1st day after irradiation	*Tumor Implant:* Increase in extravascular red haze noted (Fig. 7 *E* and *H*). Many vessels are beginning to assume a "beaded" appearance. This seems to be only a local small expansion or shrinkage and if anything the blood flow seems less. No noticeable change in the normal functional behavior of capillaries could be seen at this stage, however. *Control Chamber:* Increase in red haze noted here also, as well as the above-mentioned "beaded" appearance. No change in the normal functional behavior of the capillaries could be seen.
3-5-38 2nd day after irradiation	*Tumor Implant:* Reddish haze noticeable but seems less marked. Tumor seems to be shrinking in size although the outlines are difficult to see. *Control Chamber:* Reddish haze noticeable here also, interfering with observation of some of the blood vessels.
3-6-38 3rd day after irradiation	*Tumor Implant:* Reddish haze clearing. Flow of blood in vessels seems sluggish but vessels themselves appear to be more normal in contour. Emptying and filling seem to go on as usual. *Control Chamber:* The blood vessels in the control chamber seem to be behaving in like manner to those in the tumor implant chamber.
3-7-38 4th day after irradiation	*Tumor Implant:* A secondary red haze has developed which seems to be more marked than the immediate reaction. Observation and photography have become difficult due to loss of contrast as a result of absorption of the various wave lengths of light by the reddish haze throughout the chamber. Many blood vessels are beginning to shrink and remain empty. Some have broken up with small diffuse hemorrhages along their course while others have a thin, crinkly or tortuous course with little blood flow. Destruction of vascular pattern seems imminent in patches in different portions of the tumor chamber. The actual blood flow or total contained volume in the irradiated areas seems actually diminished. *Control Chamber:* Results similar to those obtained in the tumor implant chamber, were also noted in the control area.
3-8-38 5th day after irradiation First noticeable gross erythema	*Tumor Implant:* Chamber is so obscured by the diffuse haze (red) that observation and photography were impossible. This red haze was grossly visible for the first time since irradiation. Blood vessels were broken down and the tumor seemed to be shrinking due perhaps to resorption. *Control Chamber:* Vascular pattern in the control area seemed to be destroyed. None of the former landmarks remained visible.
3-15-38 12th day after irradiation	Chambers have failed to clear. No change from above. Gross erythema marked. Observation and photography impossible. Pictures of the whole ear showing the chamber *in situ* taken in color. Then the upper two-thirds of each ear was removed for microscopic study.

The rabbits in all seven of these experiments were all refractory to subsequent re-inoculation with tumor in the testicle. This was a common finding (70 per cent) following spontaneous

FIG. 7. Sequence of events following single massive dose of 10,000 r. *A*, low power (10×) view of the tumor fifteen days after transplantation just before irradiation. The tumor is spherical and well vascularized. *B*, control area (10×) fifteen days after operation showing almost complete healing and normal arborization of the vessels. *C* (40×). Vessel pattern at the margin of the tumor just before irradiation. *D*, the same field one-half hour after irradiation showing development of red haze around the vessels. *E*, the same field one day after irradiation showing marked increase in the red haze (which almost amounts to microscopic bleeding). Many of the vessels are empty. *F*, higher power of *C* before irradiation showing an anastomotic loop of a small vessel with its capillary branches (90×). *G*, same loop one-half hour after irradiation showing the red haze which has developed around the vessels (same as *D*). *H*, same loop one day after irradiation showing the marked increase in the haze and the reduction in the blood flow (same as *E*) (90×).

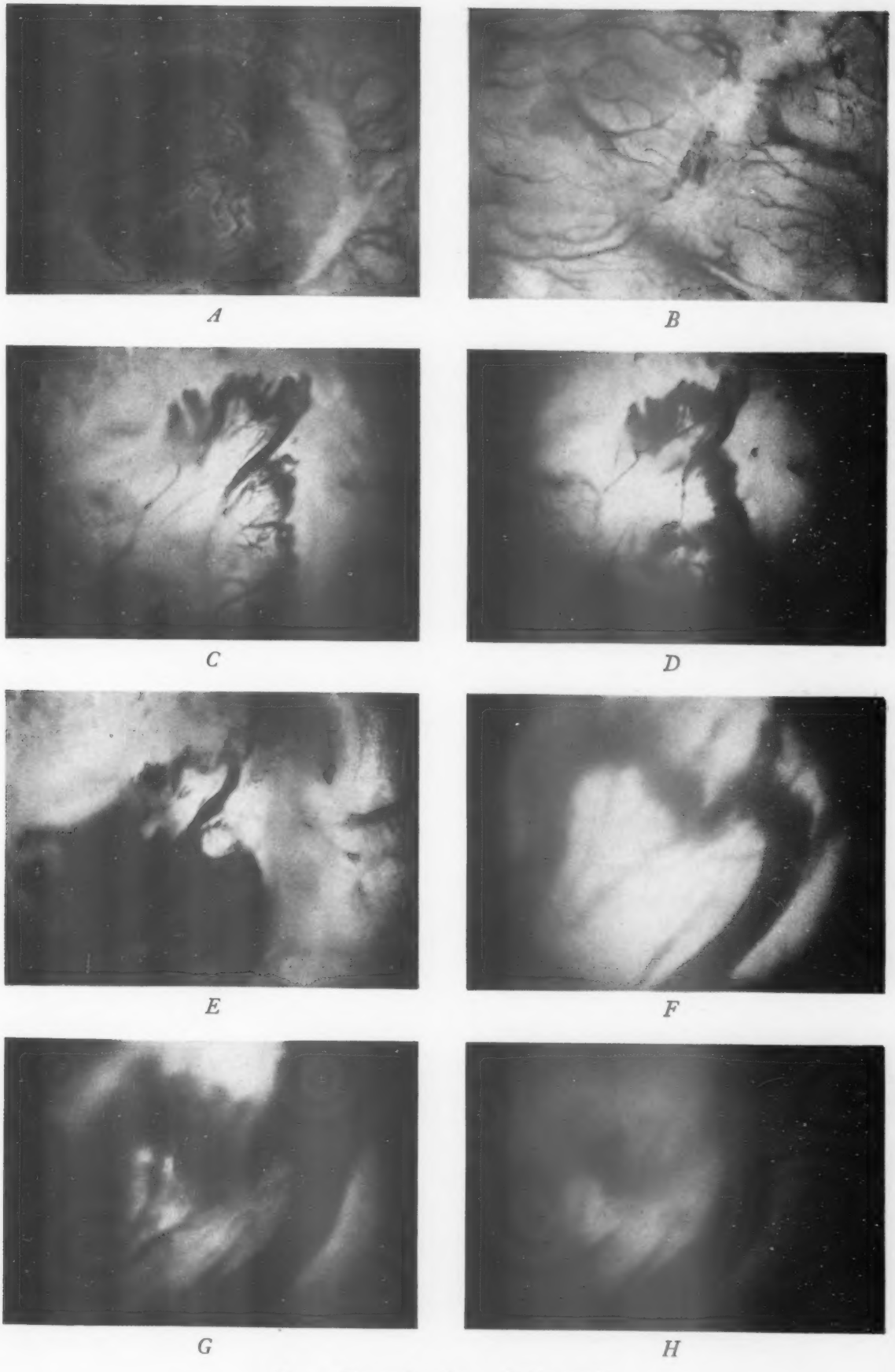

FIG. 7 (See explanation on facing page)

resorption of the tumor without irradiation in these ear chamber experiments.[15]

EXAMINATION OF MICROSCOPIC SECTIONS THROUGH THE EAR CHAMBER

1. *Non-irradiated Control Ear Chamber One Month after Operation, No. y 181.* This shows the site of operation healed, with both sides immediately beneath the window covered by a thin, yet well developed epithelial layer. There is some formation of a definite corium although the age of this preparation is not sufficient to allow for the development of much thickness. There is a well defined basal layer, the nuclei of which show a fairly large number of mitotic figures. The subcutaneous tissue is rich in capillaries and blood vessels of various sizes. The larger ones show evidence of the development of a muscular wall. Hair follicles and glandular structures have reappeared near the margin of the repair area. The staining of all nuclear structures is essentially normal.

2. *Non-irradiated Tumor Implant Ear Chamber, One Month after Operation, No. y 727.* The site of operation is covered with a thin layer of epithelium but this is, however, one or two cells thicker than that of the control site. The number of blood vessels in the tumor implant site is many times greater than that of the control. These vary greatly in size and the greater majority are only endothelial tubes. Spread in among the small capillary meshworks are the shadows and debris of the tumor cells. No actively growing or definitely viable tumor cells are found. Aside from the pallor of the degenerating tumor cells, the staining of the cells in the section is normal. In some sections viable appearing tumor cells with mitotic figures are seen. This variation in the tumor is commonly found at this stage (resorption stage).

3. *Irradiated Control Ear Chamber, No. y 175, Forty-three Days after Operation, One Month after Irradiation.* The structure here is exactly the same as the control in the number of vessels, thickness of epithelium, and organization of the connective tissue. In general all of the cells are pale, poorly stained, and ill defined. The nuclear chromatin, particularly of the basal layers of the skin, is clumped and there are large pale areas in the nucleus which take a slight eosinophilic tint. The nuclear outlines are not sharp or well-defined. The connective tissue fibrils are slightly swollen and fuzzy. They are more widely separated than usual suggesting an increase in intercellular fluid. The endothelium in the larger vessels is crinkly and their cell nuclei are somewhat swollen and stain poorly. In some cases the endothelial nuclei seem to have lost their chromatin structure leaving a dark, hazy remnant. The membrane-like endothelial wall is extremely thin (almost filamentous). Elsewhere are seen irregular collections of endothelial cell debris suggesting the site of a small blood vessel. Intermingled with this debris and nearby are frequently noted small orange-colored collections of amorphous material and shadows of red blood cells. No thrombi are noted. Polymorphonuclear and other phagocytic cells are more numerous than normal, especially in the neighborhood of disorganized blood vessels. Occasionally these cells are apparently adherent to the wrinkled endothelial walls. The nuclear material in the cartilage is likewise hazy, poorly stained, and a little swollen but seems otherwise unchanged.

4. *Irradiated Tumor Site, One Month after Operation; Twenty-one Days after 10,000 r, No. y 174.* The same general pallor and indefinite outline are visible as in the irradiated control site; the same damage to the endothelium and the same masses of red blood cells in various stages of disintegration outside of the vessels. These extravascular collections of the red blood cells are more numerous in the tumor site than elsewhere. The tumor site is occupied by a few dim shadows of tumor cells in all stage of disintegration. Organized clotting or thromboses are not seen. No tumor cells can be clearly seen and there are no mitoses. In some places the vessel pattern is very much like that seen *in vivo* with large numbers of parallel branches of small vessels almost in contact with each other because of the dissolution and disappearance of the tumor cells. There is less evidence of the presence of tumor in these sections than in the unirradiated resorption stage of the same age, probably as a result of its rapid dissolution following the irradiation.

DISCUSSION

In general, the development of the vascular reactions taking place in the normal control area corresponds closely to those reported by the Clarks and their coworkers and to the previous experiments in this laboratory.[6,15] The presence or absence of

tumor in the right ear seemed to have no effect upon the vascular reactions of the left (control) ear. Slow progressive repair with gradual vascularization centrad from the periphery of the operated areas was noted in all cases, with less profusion of capillary growth in the control sites as compared with vascularization in the tumor implanted chambers.

Efforts were made to observe the changes in frequency and the extent of the normal periodic filling and emptying of the capillaries in the control areas and the tumor growth ears, but no periodicity was noted. The mechanism controlling these erratic changes in blood flow was not apparent.

Perhaps partially due to the difference in operative technique and chamber size and partially to the lessening in growth rate of the present tumor in comparison with the tumor in former years, sinusoid formation was practically negligible at the periphery of the growing implant. In fact, all of the capillaries both in normal repair areas and in tumor implanted areas seemed to be of somewhat smaller caliber than those photographed by Ide *et al.*[15] Postoperative hemorrhage and secondary hemorrhage occurred in the normal repair area but with less severity than in the areas in and surrounding the tumor. This was probably due to the relatively large size and greater number of fragile vessels in the tumor. Corona-like vascular arrangement around the tumor edge and a definite change in direction of the blood vessels from a centrad to a peripherad direction, due possibly to the centrifugal direction of peripheral tumor growth, was noted as before. Since there was no change in vascular response in either the control or tumor implant sites from that previously reported,[15] abnormalities described after irradiation were probably due to the effects of the irradiation. These changes are probably not specific for roentgen irradiation alone, but may in whole or in part be noted after other types of injury (ultraviolet, heat, chemical, etc.).

The almost immediate development (within one hour after irradiation) of a diffuse redness around the blood vessels was unexpected since no gross change could be noted in the vessels and the walls of the capillaries showed no visible patencies. However, a transitory erythema or blushing has been reported clinically to occur within the first four to twelve hours after large single massive dosage. In view of the observations of Michels and a study of our own fixed sections, it seems likely that this diffuse redness around the blood vessels is due to the extravasation of erythrocytes and plasma from the blood vessels through the damaged endothelium. Under the present circumstances it is impossible to say whether the endothelial cells contract away from each other, or become torn and fragmented as an acute reaction to the irradiation. The bead-like appearance of the capillaries shortly after irradiation might indicate a considerable direct effect of the radiation upon the endothelial cells while the complete breakdown of the vascular pattern within a week after irradiation leaves little doubt that such is the case.

As a result of these observations, there seems little doubt concerning the validity of the contention of many experimenters that primary damage to the blood vessels is an important factor in radiation effects upon tumors. Since the changes described above occur in the blood vessels of both the control and tumor tissues this effect upon the endothelium is not influenced by the tumor. There are innumerable observations reported (mainly histological) upon the direct effects of radiation upon the tumor cells. It is obvious from these observations that the part played by the changes in the blood vessels may have immediate summative effects as well as lasting summative effects upon tumor growth and survival.

We realize that 10,000 r is a high massive dose, yet in experiments being carried on in this laboratory by Dr. Sidney Larson (unpublished) *in vivo* massive dosage of this amount has not always been lethal for this

tumor. The dosage is large enough, however, to yield pronounced blood vessel effects. The effects of smaller doses (massive and fractional) will be reported later.

The failure of a gross erythema to appear within the first five days and its sudden appearance and progression from this time on is probably related to the fact that the endothelium in general retains its integrity and tonus up to the fifth day. After this, a general dissolution of capillary structure begins with rapid diffusion of red blood cells and plasma into the tissues nearby. This is followed by a slow recovery of tone in portions of the wall which results in the beaded, crinkly appearance noted above. About this time blood flow reappears in the larger vessels although the flow never regains its normal volume during the period of observation following irradiation (twelve to fourteen days). Many vessels are not filled again so the tumor cells supplied by them must, of necessity, remain dormant or die even if they may not be directly damaged by the irradiation. The erythema (gross) is thus an extravascular manifestation rather than being due to an increased blood flow in the vessels themselves or an increased number of patent vessels.

SUMMARY AND CONCLUSIONS

1. Actively growing Brown-Pearce rabbit epithelioma with well established circulation in the tumor ear chamber, and the control ear chamber, were irradiated with 10,000 r and the *in vivo* reaction of the blood vessels studied in seven rabbits.

2. Almost immediately after irradiation (within an hour) a red haze developed around both the tumor and control vessels which became progressively more marked microscopically but the gross erythema did not appear until the fifth day after irradiation. At this time the tissues were so obscured by the diffuse redness (extravascular red blood cells) as to make further microscopic study impossible.

3. Within a few days after irradiation the blood vessels in the tumor and control sites became beaded and irregular in contour. The flow was restricted and erratic, many vessels remaining empty. The normal responses to paling and flushing were almost intact.

4. By the end of the fifth day after irradiation a gross erythema developed and the finer details were obscured. Blood vessel and capillary dissolution began at this time with a slow recovery over the following week. Many large vessels (as well as small ones) never refill with blood after this.

5. Although the erythema is a direct result of damage to the blood vessel endothelium by the irradiation, the color is due to the presence of red blood cells in the perivascular structures. The redness does not become visible to the eye until a large amount of blood has collected in the extravascular spaces due to vessel dissolution.

6. The reaction in the endothelium from the irradiation is the same in both the control and tumor vessels so that the tumor growth does not change the endothelium in this regard even though it calls forth a more active vessel proliferation than does the repair reaction.

7. All seven of the animals developed refractory states to re-inoculation after the destruction of the tumor by the irradiation.

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THE EFFECT OF ROENTGEN RAYS UPON BACTERIOPHAGE

STUDIES IN BACTERIAL METABOLISM. CXI

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THE discovery by Roentgen that x-rays will penetrate deeply into living tissues and make visible denser structures, as bones, and reveal imbedded foreign bodies as missiles of warfare very naturally attracted attention to the possibility of utilizing these rays in treatment of microbic infections of the body. Some promising clinical results have been reported, and, logically, attempts have been made to correlate these with direct effects of roentgen rays upon naked bacteria, viruses and substances of bacterial origin without intervention of cellular structures. Judging from the literature it may be said that the results of such direct exposure of bacteria and viruses to roentgen rays and even to radium emanation have been disappointing in general. Bacteria and viruses do not appear to be harmed materially even after exposures that would be unendurable by the human body. It would seem from these experiments that the smaller the biological particle exposed to roentgen-ray bombardment, the less effective is its action upon each exposed unit. Several theories have been advanced to account for this noteworthy contrast between facile tissue penetration by roentgen rays and their microbicidal ineffectiveness. Perhaps the most widely accepted of these is the "target" theory, stated by Mohler and Taylor[8] thus: "The effects of x rays in liquids are localized in 'columns of ionization' along the path of each high speed electron. It is assumed that biological effects are produced in these columns. Cathode rays of 155KV give an area of 0.68×10^{-10}cm^2: x rays of wave lengths 0.56 to 4 Ångstroms* give values (areas) between 0.72 and 1.6×10^{-10} cm^2. A particle 0.2 microns in diameter has a 50–50 chance of escaping a dose of 100 r. Ultramicroscopic particles have an even chance of escaping a dose of 1,000,000 r. The passage of a "column of ionization" (the path of an electron) through a bacillus is in general nonfatal; the column must pass through a particular point to cause death[11].† Crowther[1] has developed this "target" theory somewhat in greater detail. He states: "The beam of x rays consists of a swarm of protons. The energy of each proton is proportional to the voltage at which it is excited." This theory reëmphasizes the discontinuous nature of roentgen-ray emission and assumes that action takes place whenever a biological structure (bacterium or phage particle for example) is hit by radiation. "A hit is registered whenever a pair of electrons is produced anywhere within the sensitive particle." According to this "target" theory microscopic particles have a very fair chance of escaping the effects of radiation simply owing to the (relatively) wide distances which separate points at which energy is concentrated. Therefore it would appear that missing the "target" is a prime cause for failure of roentgen-ray bombardment of particles of small size (bacteria or phage) rather than insufficient energy or unsuitable state of the projectiles to inflict damage "since a single quantum of x ray radiation has sufficient energy to produce some hundreds of ions in tissues in which it is absorbed." The tenability of the "target" theory lies in a tacit admission that roentgen rays are physically capable of producing lethal effects in microscopic and submicroscopic biological entities even if their full effectiveness is never realized because of the (mathematically) inherent

* An Ångström unit is 10^{-8} cm.

† For a more complete discussion of the mathematics involved in the "target" theory see Pugsley, Oddie and Eddy.[9]

large proportion of "misses" (and possibly ineffective, glancing blows). One weakness of the "target" theory is its failure to recognize that "misses" which explain failures logically postulates "hits" which imply successes, if the roentgen-ray bombardment could be made sufficiently dense or accurate to insure that each bombarded particle should eventually be in position to receive a direct hit. However, the experimental difficulties of producing convincing proof, if any, of inaccuracy of the mathematical assumptions involved puts the burden of proof on the opposition.

Bacteriophage, regarded by many observers a member of the group of filterable viruses, possesses several characteristics peculiarly favorable for experimentation with roentgen rays. It is filterable; it is produced only in presence of living cells; it is exquisitely species specific. Also it can be generated consistently without use of experimental animals. It is extremely potent and its potency can be measured by the dilution method in multiples of 10. Finally, it is inactivated by physical or chemical agents, and inactivation proceeds progressively.

The published literature on the effects of roentgen rays on bacteriophage is scant. Mizuno,[7] however, made extensive comparative studies of the effects of roentgen rays and of ultraviolet radiation upon phage. He states that roentgen rays, unlike ultraviolet radiation, have no appreciable effect upon bacteriophage. Beckwith, Olson and Rose[1] found that bacteriophage exposed to roentgen rays at a distance of 30 inches was little changed even after relatively long exposure. Wyckoff[13] expressed the view that the lethal effects of roentgen rays and of ultraviolet radiation were not the same. Wright and Kersten[12] state that soft roentgen radiation (at 1.54 and 1.38 Å) had little effect on phage after one hour's exposure, but that after five to six hours' exposure the effect was somewhat greater. Even after long exposures of bacteriophage to radium emanation little or no lethal effect is noticed. Bruynoghe and Mund[2] kept typhoid phage in contact with 7–8 millicuries of radium emanation for five days without detecting loss of titer and Spencer[11] found that certain bacteria were resistant to radium emanation. The general impression held at present appears to be reflected in the observations of Schepmann and Flecke[10] who state that the longer (softer) roentgen rays are more effective lethally than the shorter (harder) roentgen rays. Equal doses of hard rays produce only half the effects of soft rays upon cultures of staphylococcus, *B. coli*, *B. pyocyaneus*, *B. prodigiosus* and *B. mesentericus*. (See also Pugsley, Oddie and Eddy[9].) The statement made by Kaye[6] several years ago is significant: "Curiously enough the rays (x rays) have little effect or no effect on bacteria or their spores, and in this respect stand out in marked contrast to ultra-violet light."

EXPERIMENTAL

a. Bacteriophages Used in These Investigations. "Pure" bacteriophages, that is phages freed from practically all associated protein-like substances and containing about 0.5 mg. nitrogen per 100 cc. were prepared, according to the procedure of Colwell,[3] for *B. coli*, Flexner and for *Staphylococcus aureus*. These phages were suspended in distilled water and filtered through Berkefeld filters. Their titer was 10^{-8}; that is to say, they contained 100,000,000 phage particles per cubic centimeter. They retained this titer during the entire time of experimentation.

b. Technique of Exposure of Bacteriophages to Roentgen Rays. The phages were exposed in uncovered Petri dishes (of Pyrex glass) in layers 0.6 cm. deep. The total volume was 20 cc. The Petri dishes were placed exactly 12 inches from the cathode. The energy output of the roentgen machine was determined accurately for this distance. It was 20,000 r in twenty-five minutes. A photographic plate exposed at this distance showed that the area of maximum emanation covered a circle 6 inches in diameter. Outside this circle the intensity of emanation diminished considerably. Inasmuch as the diameter of the Petri dish which contained the phage was 4 inches, and the dish was accurately centered for each exposure, the full force of the roentgen rays should have been received by the

phage each time. No detectable rise in temperature was noted during exposures. The duration of exposures was from ten to thirty minutes—8,000 to 24,000 r. Phages in open Petri dishes were the controls, unexposed to roentgen rays. After exposure the phages were filtered to eliminate possible incidental contaminants. The filtrates were then tested for potency in the usual manner by serial dilution in multiples of 10.

c. Rotation of Bacteriophage. Having in mind the "columns of ionization" referred to above, an attempt was made to increase the chances of "hits" by rotating the Petri dishes within the area of greatest intensity of emission eccentrically (1 cm. off center) on a slowly turning phonograph disk rotator, during the entire time of exposure. By so doing it was hoped (remotely) that the effects of these "columns of ionization" might be increased in the aggregate through reduction of the chances of "misses"—that is to say, futile bombardment of empty areas—and that the existence of these columns might be inferred by a difference in titer between phages exposed to bombardment, still and rotated respectively. These phages were water clear and therefore the shielding effect of alien substances was minimal. There should be little protective action of one phage particle for another over a period of thirty minutes (the time of maximal exposure). Each of the 100,000,000 phage particles in each cubic centimeter of solution exposed to the roentgen-ray bombardment should have ample opportunity to be hit at least once. Finally, the method of serial dilution, titrated in multiples of 10, is sufficiently precise to register inactivation of a significant number of phage particles.

RESULTS

The results of exposure of several "pure" bacteriophages, including both separate species and separate preparations of each species of phage, to the action of roentgen rays (24,000 r during thirty minutes' exposure) were negative. The titer of the phages, rotated or unrotated, was not significantly reduced. It is worthy of note that the glass of the Pyrex Petri dishes was permanently browned as a result of these exposures. In light of the rapid and complete inactivation of these same phages exposed to ultraviolet radiation, reported elsewhere, the conclusion is drawn that roentgen rays (24,000 r in thirty minutes) have no significant effect upon bacteriophage.

DISCUSSION

The results of these experiments are in accord with those of other investigators. They indicate that roentgen rays are not significantly phagicidal. Also they redirect attention to the rather widely accepted "target" theory which has been advanced to explain the phagicidal ineffectiveness of roentgen rays. The "target" theory assumes in essence that biological effects of roentgen rays are produced along "columns of ionization." These "columns of ionization" have a cross section (area) of from 0.72 to 1.6×10^{-10} cm^2. In the theory this area is compared with the area (cross section) of a microbe or an ultramicroscopic particle. Phage particles (which are ultramicroscopic and of the order of 30 to 50 millimicrons in diameter) suspended in a liquid medium are small enough and far enough apart at a given level to permit "columns of ionization" to pass between them: to miss them, in other words. This concept is two dimensional whereas actually the field of experimental activity is three dimensional with time as a fourth dimension. In other words, the depth of the phage layer and the time of its exposure to the roentgen-ray bombardment are equally important with the areas of "columns of ionization" and of phage particles. Phage particles are electrically charged; also they should show brownian movement. Being very small they mutually repel each other. Consequently they tend to be disseminated uniformly in the suspending liquid. This repellent action is three dimensional. The combination of repelling force and brownian movement should preclude the probability of phage particles at different layers (each layer one particle deep) being in vertical alignment. Rather their distribution should be staggered; that is to say, particles at one level

(or layer) would tend to occupy interspaces between particles at higher and lower levels and so throughout the entire depth of liquid there would be a continuum of particles rather than columns of particles with vacant interspaces. Therefore, it would seem to follow that roentgen rays ("columns of ionization") should encounter more phage particles than spaces between particles in a layer 6 mm. deep. It will be recalled that the phages used in these experiments contained 100,000,000 particles per cubic centimeter. Yet after thirty minutes' exposure to roentgen rays (24,000 r) these phages, still or rotated, failed to show any significant inactivation. These experiments do not, of course, disprove the "target" theory. They do seem to indicate, however, that roentgen rays fail to inactivate bacteriophage within reasonable periods of time because they are inherently not phagicidal rather than that they fail to inactivate phage through poor marksmanship. These experiments are not to be construed as casting doubt upon the clinical value of the effectiveness of roentgen rays in treatment of disease within the body. Here the conditions are complicated and beneficial effects may be due in no small degree to stimulation or reinforcement of body defensive mechanisms (as liberation of enzymes from lymphocytes) remote from the foci of infection.[5]

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CHEMICAL STRUCTURE AND ITS RELATION TO GROWTH AND DEVELOPMENT*

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THIS is largely a statement of principles, such as is at times useful.

The healing art has two aspects—the immediate and the remote. The immediate is the relief of the sick. This is the function of the physician. The remote is the determination of the processes which underlie sickness. This is the function of the medical scientist.

The physician must perforce work from without inwards. From symptoms to their elimination. The medical scientist must work from within outwards. From the nature of being to its distortions and disturbances. It is necessary that the medical scientist be acquainted with the outer manifestations of the inner aberrations. It is useful for the physician to have insight into the possible inner bases of the symptoms he is attempting to alleviate. The acquisition of this insight is a long and laborious process. It depends upon the labor of the medical scientist and the clarity with which he can tell of his work and thoughts.

The present occasion is an attempt to set forth and to establish a point of view with respect to a natural phenomenon of general occurrence—namely *growth*. The subject is pertinent since no little attention is paid by roentgenology to tracing growth changes and to the correction of disturbances thereof.

Now it is obvious that progress in the study of growth, as of any process of nature, is more solid and more productive if the study is based on the four principal aspects of living things: direction, substance, state of substance, and form.[1]

Within the science of genetics is comprised the *direction* of growth, the determination of what course the development of living shall take. What substances shall be used not only to express the specific growth progression of any particular organism but also to compose the material thereof. What states these substances shall have for the activity of growth. And into what structural configurations they shall be combined in the production of the mature organism.

Within the science of chemistry is comprised the *substance* of living. The reaction basis of growth is founded in the chemical composition of its substance. No interpretation of any growth process is adequate until the nature of the chemical participants and determinants is known. No explanation can be finished until the responsible chemical reactions have been set forth.

Within the science of physics is comprised the *state of substance*. The state of substance is concerned with the rate and extent of growth activity. It is responsible for the reference frame of time. Such states as reside in permeability, imbibition, conduction, viscosity, the electrodynamic field, and cognate phenomena are sufficient examples of physical factors concerned in the acquisition and maintenance of that state of substance which is essential for growth.

Finally, within the science of anatomy is comprised that which deals with *form*. The form which substance takes in growing things. The shape, the arrangement, the juxtaposition, the connections, the extensions and the compressions of substance are the elements of anatomy. Within this science is comprised all that is concerned with architecture and structure; all that is concerned with space displacement and

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configuration as carriers of growth expression.

Thus, to recapitulate:

The direction of growth is the concern of genetics; the substance and expression of growth is the concern of chemistry; the state of growth substance is the concern of physics; and the form of growth is the concern of anatomy.

The immediate interest is with the substance or chemistry of growth and its relation to the several expressions thereof.

A definition of growth is indicated.

Now, growth is not single—it is multiple. It is the combined expression of developmental and incremental factors and processes.[2]

It is anlage formation as much as it is cell increase in number.

It is increase in cell specialization or differentiation as much as it is increase in cell size.

It is segregation of these cells into functioning tissues or organization as much as it is accumulation of mass of functionable substance or anabolism.

Indeed and in fact it is all of these—the summated expression of all those integrated processes which serve to produce the structurally and functionally mature organism.

If it be admitted that the reaction basis of growth is founded in the chemical composition of its substance; and if it be admitted that growth is not single but multiple, then it follows that each and every separate and specific growth process has its own particular set of chemical determinants, participants, and reactions.

No one would claim, I am sure, that the chemical processes concerned in cell division *per se* are the same as those which are responsible for the production of a bone cell from mesenchyma.

The participants of growth are of course the naturally occurring chemical constituents of tissues.

Knowledge of the chemical nature of the determinants of growth is increasing daily. One has but to glance at the multiplicity of titles relating to the auxins—or stimulants of plant cell elongation—to realize that interest in the chemical conditioners of growth is today a very lively subject. Indeed, it is beginning to partake of the aspects of a bandwagon on which many an amateur tootler is climbing with unseemly haste.

With one possible exception—namely, that of the sulfhydrylsulfoxide equilibrium in proliferation—we know nothing of the immediate chemical reactions of growth.[3]

Now the properties—and hence the reactions—of chemical compounds are determined not only by their component atoms but also by the way in which these are arranged in the molecules. That is to say, in the domain of pure chemistry the structure is as important as the constituents. Therefore, since growth is an expression of reactions between chemical compounds; and since each growth activity has its own set of chemical determinants, participants, and reactions; and since differences between compounds resolve themselves into differences in structure as much as into differences in composition, it follows that any inquiry into the chemistry of growth must eventually resolve itself into an inquiry into the relation of chemical structure to growth and development.

A priori, then, the functions of chemical compounds in growth are conditioned by their structure.

The argument has now laid the foundation on which this topic can be developed.

Logic demands that the development be along three avenues of approach, namely, that of the participants, that of the determinants, and that of the reactions.

For purposes of simplification I will confine discussion to the components of the cellular proteins—the cytoplasmic and the nuclear. To the amino acids and the purine and pyrimidine components of nucleic acid.

These are chosen for three very important reasons. They comprise the bulk of living matter of all organisms. They provide the reaction basis for living, of which growth is a chief property. And they are

the naturally occurring chemical constituents of living tissue of general distribution.[4]

Concisely, they are the "Baustoffe" of growth wherever expressed.

Chemical structure is a significant factor with respect to the compounds used in tissue building.

It has been known almost from the beginning that the amino acids as they occur in nature have a definite configuration with respect to polarized light. Some turn it to the right and some turn it to the left. Strangely enough, many organisms seem to reject or to be unable to use the isomers of these naturally occurring compounds. To be utilizable the amino acids must have the same structural relationship to polarized light as those found in proteins.

Chemical structure thus determines the availability for growth of a large class of fundamental compounds.

Now the growth process which takes an entodermal cell and makes a liver cell out of it, and takes a mesenchymal cell and makes a muscle cell out of it is called "differentiation." The two kinds of cells are recognizably different in structural make-up even though both are built of amino acids. Analysis supports observation that the chemical structure of the protein molecule of the liver cell is distinct from that of the muscle cell.

Thus, differentiation is really a chemical specialization of the cell structure. Without this specialization there could be no distinction between cells; no differentiation phase of growth.

This difference lies in no small degree in the difference in proportion and arrangement of the constituent amino acids. In addition the chemical nature of the amino acid unions is most important to protein structure.[6,7] Indeed, it is possible that differences in these are real factors in establishing differences between many proteins.

Without doubt chemical structure is an influence in determining what the product of differentiation growth shall be.

Roentgen studies show that molecules tend to arrange themselves with regularity into a definite space lattice pattern which is characteristic for any given molecular type.

It is also a common property of molecules in combination to assume structural forms which are characteristic. Thus urease has one shape and hemoglobin another.

There is no reason to assume that the forces which determine these arrangements are abrogated when molecules are built up into living tissue.

It is, therefore, not impossible that the factors which contribute to definitive structural arrangements outside living tissue also contribute to the forms which living tissue takes as it is built of the characterizing molecules.

That is to say, the idea can be entertained that the structural nature of the molecules which are used in tissue growth may well condition the shape which the growing part may take.

This morphogenesis is really expression of cell segregation which is called "organization" by the biologists. It is therefore possible that chemical structure conditions the product of organization as it does that of other growth activities.

These are but brief suggestions as to how the chemical structure of the building blocks of tissue is significant to growth through determining their availability and how through them it is significant in the production of differences in cell type and form.

Although the amino acids and other nitrogenous components of living tissue of general distribution function as building substance and energy, they also function as contributors of specific reaction properties to the protein molecules into which they are incorporated by the processes of growth.

But even more than this is the probability that each of these compounds plays a specific part in the regulation of some growth activity. The distinction here is between function as a component of tissue and function as a determinant of tissue; between the part played in providing the

reaction basis and the part played in activating and conditioning the expression of the reaction basis.[4]

An inquiry along this line has been going on at the Lankenau Institute for eleven years. As would be expected from the argument of the preceding paragraphs a relation between the chemical structure and the growth effect of these compounds has been traced in some instances. A few of these will be given to demonstrate the point.

In a growing organism part of the ingested food goes to produce new tissue and part to produce energy. When—other things being equal—energy expenditure increases, the amount of material used for growth is cut and mass increase is reduced.

Now it happens that the specific dynamic effect of glycine is less than that of alanine, and the specific dynamic effect of aspartic acid is less than that of glutamic acid. And alanine and glutamic acid differ from glycine and aspartic acid by having one more CH_2 in the molecule. The indication is that the added CH_2 is a determinant of the increased stimulation of energy expenditure by these particular compounds.[8–11]

Hence the chemical structure of glycine and aspartic acid in relation to alanine and glutamic acid is significant to growth in that the CH_2 difference influences the regulation of energy expenditure, which—in the growing organism—strongly factors the amount of material available for mass growth.

When an OH group is introduced into the molecule of some of these naturally occurring tissue components of general distribution quite an effect is produced.

Thus tyrosine is less toxic than phenylalanine and forwards differentiation.[9]

Hydroxyproline is less toxic, has less specific dynamic effect and forwards differentiation at lower concentrations than does proline.[12,13]

Serine is less toxic than alanine, has less specific dynamic effect, and may exhibit a special influence on differentiation.[9,14]

Finally thymine, as compared with cytosine, is less toxic and enhances differentiation to greater extent.[15,16]

Thus, the introduction of the OH group into these four compounds acts to forward growth indirectly by reducing toxicity. It acts directly in the case of tyrosine, hydroxyproline, and thymine by conferring on them an added facilitation of differentiation.

Just because the OH compounds are better differentiation agents than the same compounds without the OH does not mean that OH as such is the differentiation effective agent. What is probably true is that the introduction of OH favors the formation of an effective configuration in intermediary metabolism.

Evidence suggests that this is pyrrolidone or some part or derivative thereof. This comes from the fact that a chemical relationship between the compounds which forward differentiation can be traced through this configuration.[17]

This brief exposition is sufficient to demonstrate the part played by chemical structure in the determinants of growth.

Turning now to the significance of chemical structure to the reactions of growth it is obvious that since the substance of growth is chemical and the processes of growth are expressions of reactions between chemical molecules or groups, the structure of these molecules and groups should be of particular importance.

Now it has been found that when a hydrogen of an amino acid such as alanine is replaced by a sulfhydryl, the compound may act as a stimulus to cell increase in number. The molecule may be single as cysteine or in combination with others as in the tripeptide glutathione.[18]

When it happens during the normal course of physiological oxidation activity that two such groupings unite with loss of hydrogen to form a disulfide in cystine-like union, the compound is no longer an active stimulant to cell multiplication.

And when this normal oxidation trend continues so that there is produced a compound in which the sulfur carries an oxygen

not only is there no stimulation of cell multiplication, there is even the opposite effect, a retardation of cell increase in number.[3]

Thus the chemical structure which develops during the normal course of living activity determines what the subsequent reactions shall be, which in turn determines what shall be the nature of the growth response. The change in chemical structure brought about by chemical reaction with the environment determines whether a basic type of growth expression shall be forwarded or held back; shall continue or shall cease to exist.

Although this principle has been demonstrated only with the sulfur groupings it cannot be doubted that all other growth activities are similarly conditioned. It must be so since the laws which govern chemical change in general must also govern the chemical changes of growth. And this principle is but the expression of the Second Law of Thermodynamics as extended to the Law of Mass Action. Which is in essence that the products of a chemical reaction tend to retard its further progress.

The foregoing paragraphs have given in all too brief survey the significance of chemical structure to growth and development. They have pointed out how structure is a *sine qua non* of the substance of growth; of the determinants of growth; and of the reactions of growth. If they stimulate intensive analysis of the substance of growth before and after its incorporation into living tissue in order that the nature of growth may be more accurately traced, they will have fulfilled their purpose. The stimulus can hardly have been delivered to a more appropriate spot since roentgen-ray analysis is the present basis of such information and roentgenology the science of its application.*

* For discussion see page 279.

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Vol. 43, No. 2

RADIATION, MUTATION AND THE GENE*

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GENES are the units of heredity. They occupy somewhat the same position in genetics as atoms do in chemistry. Genetic formulae are written with genes, chemical formulae with atoms.

Biologically speaking, genes are minute structures located in the nuclei of cells, normally in definite and linear arrangement on the thread-like bodies called chromosomes which condense into rods at cell division. Genes segregate and recombine in successive generations without losing their identity and exert a regulating influence on the developing individual so that it possesses the characteristics of its species or any hereditary variations from these characteristics derived from its ancestors.

Two complete sets of genes are present in all body cells (nerve, muscle or epithelium) and one set in the germ cells (egg or sperm). All body cells of a given individual are similar to each other in possessing the same set of genes derived from the fertilized egg. Each gene is named according to its most obvious effect but in reality each has many different effects, some structural, some functional. There is no evidence that any gene influences one trait alone. Every character, however simple, is dependent for its existence upon a number of genes. When the geneticist speaks of a gene for feeble-mindedness he recognizes that even a feeble mind must result from the interaction of many genes all but one of which are genes for normality. The exceptional gene by which it differs from normal is the one designated as the gene for feeble-mindedness. It has been possible to study by genetic method only those genes which have mutated, leaving the great majority hypothetical.

Mutations or hereditary changes may be divided into two classes according to their effects: (1) "visibles," which change traits such as color, size, behavior, longevity, resistance to disease, structure of external or internal organs, and (2) lethals, which cause death of the individual at some stage in development. H. J. Muller in 1927 showed that roentgen rays increased the occurrence both of visibles and of lethals up to two hundredfold. These induced mutations are similar to those occurring spontaneously. Definite desired mutations cannot be produced at will. We cannot aim at a single gene and cause it alone to mutate, but we can often select from the multitude of changes produced those that we desire to perpetuate and study.

Three types of chromosome and gene behavior may be listed as concerned with mutation: (1) loss or addition of whole chromosomes (radiation has played little or no part in this type of change); (2) rearrangements or losses of parts of chromosomes; (3) changes, probably chemical, within the gene itself.

Mutations of the second and third types are induced by irradiation. Those of the second type are considered in some detail as they have thrown much light on gene behavior and are highly important in radiation studies.

Representing by large letters the gense in two of the chromosomes derived from the mother and by small letters the corresponding or homologous genes from the father, the normal arrangement may be expressed as follows:

A.B.C.D.E.F.	*L.M.N.O.P.Q.*
a.b.c.d.e.f.	*l.m.n.o.p.q.*

Irradiation may cause deletion or loss of a

* Read in a Symposium on Growth at the Thirty-ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 20–23, 1938.

portion of one gene strand or inversion may occur as follows:

A.B.C.D.E.F. *L.M.N.O.P.Q.*

Deletion Inversion

a.f *l.p.o.n.m.q.*

A portion of one chromosome may be translocated to a non-homologous chromosome and this is usually a reciprocal exchange.

A.B.C.D.E.F. *a.b.c.d.N.O.P.Q.*

L.M.e.f. *l.m.n.o.p.q.*

Changes of these various types result in very irregular distribution of hereditary material in the formation of the germ cells, and the fertilized eggs may fail to develop or may develop into weak or abnormal and genetically unbalanced mutant types in whose descendants the condition continues.

It was formerly thought that genes functioned independently of their arrangement in the chromosomes, that no difference would be caused by rearrangement provided that the same set of genes was present. It now appears that certain genes undergo a "position effect" when they are brought into a new arrangement in the chromosomes. Thus as a result of inversion the gene *E* may be brought close to gene *A*. *A* then has a "position effect" on *E* changing it to *E'* so that its influence on a certain trait is modified. The chemical

A.B.C.D.E.F. *A.E'.D.C.B.F.*

interactions appear to change with change in position. This is a type of mutation. When the modified gene is returned to its former environment it returns to its old behavior, a reversionary mutation. The influence, then, of new gene neighbors is temporary.

In addition to the above-mentioned gross chromosomal irregularities, there may be deletions of single genes, *A.B.D.E.F.*, or minute inversions, *A.B.D.C.E.F.*, or additions by translocation of one or two genes only, *A.B.C.N.D.E.F.*, so that some have thought that all mutations are rearrangements of chromosomal materials. The majority of geneticists, however, still appear to favor the view that chemical changes within the gene, mutations in the narrow sense, likewise occur.

Until very recently students of the physical basis of heredity were dependent for their cellular material on the minute chromosomes as seen in dividing cells, but since the discovery by Painter in 1933 of the significance of the giant salivary gland chromosomes of *Drosophila*, two hundred times as large as those previously studied, it has been possible to see the minute location of the genes if not the genes themselves. These chromosomes appear as cross-banded cables made up of chromatin fibers, the bands being formed by minute granules (genes?) on the fibers. Each cable is double (derived from a fused pair of homologous chromosomes) with homologous bands of granules apposed so that it becomes relatively easy to see if any of the bands in one of the homologous (parental) chromosomes are missing or displaced. Thus chromosomal abnormalities may be minutely and directly observed.

What can be said of the nature of the gene itself? Estimating from genetic data the number of genes in the sperm or egg of *Drosophila* to be about 2,000, Morgan, Bridges and Sturtevant in 1925 supposed the diameter to be from 2 to 6×10^{-2} micra or slightly larger than a molecule of hemoglobin. More recent studies, based on mutation rate under the influence of radiation and also on observation of bands in salivary chromosomes, estimate the number in egg or sperm of *Drosophila*, to be 5,000 to 15,000, the size from 2.5×10^{-3} to 1×10^{-14} micra and the structure that of a single large protein molecule over five times as long as thick, or of several (15?) protein molecules.

As regards different kinds of genes, Gowen and Gay (1933) from mutation rate in roentgen studies of *Drosophila* divide genes into dominant vitals, 52.7 per cent; recessive vitals, 39.5 per cent; dominant visibles, 0.6 per cent; recessive visibles, 7.2 per cent. This statistical analysis does

not tell us whether the vital factors might produce visible changes if they varied in some other way or whether the genes giving visible changes are necessary to the life of the organism.

Some genes are of the eversporting variety, mutating very frequently while others are known to have changed but once. Some have mutated several times in the same way while others have mutated in a great variety of ways. One gene for eye color in *Drosophila* has undergone at least ten changes from wild type giving different colors and there are two different wild type forms of this gene known which differ only in their direction and rate of mutability. Some genes are known to take dozens and probably hundreds of different forms, as one for bristle distribution and number in *Drosophila* and one for kernel coat color in corn. However frequently changes may occur they are discontinuous, like changes in chemical molecules, rather than continuous like variations in a mass of material. In comparing changes in genes with chemical reactions it is to be noted that we deal not with a mass of independently changing molecules in a test tube, but with a mass of descendants of a single changed molecule, descendants through a succession of autocatalytic reproductions corresponding in number to the number of cell divisions necessary to form the individual or the succession of individuals.

Radiations produce mutations, probably because they can get directly at the germ plasm without too great injury to the protoplasm in general. Within the roentgen-ray range, wave length seems to make no difference, nor is intensity during treatment an effective factor. Total dosage is what counts and mutation rate increases with increasing dosage on the average in a straight line logarithmic curve. If, however, gross chromosomal abnormalities are separated from very localized or single gene changes, the frequency curve for the former tends to slope down with increasing dosage relative to that of the latter which slopes up. It appears that changes in single genes are caused by single hits while two hits are necessary for translocations or inversions, hence the difference in the type of curve. If mutation rate is low, as when dosage is low or in spontaneous changes, the chance of two breaks occurring at the same time in the chromatic threads of one cell is very slight. A single broken thread will unite again where it was hit and so there is a localized change only, and there will be practically no chance for union of two different threads.

Dosages of 2,000 to 5,000 r are convenient for producing mutations. After 10,000 r there is a dominant lethal change of some sort produced in practically every sperm cell. Dosage for egg cells must be much higher for the chromosomes are not so closely packed together and apparently the closer the packing the better the chance for irregular recombinations. Dry seeds stand a much higher dosage than sprouting seeds with cells undergoing divisions but since lethal changes are relatively low in the former, it is better to use the more resistant material in order to obtain a maximum of viable visible changes.

Ultraviolet radiation is effective in causing mutations but there is here the difficulty of getting the rays into the germ plasm without too much superficial injury. Pollen cells in a single layer can be conveniently treated and ultraviolet radiation has a different effect than roentgen rays, causing no increase in translocations, but producing many single point mutations. A further difference is that ultraviolet radiation applied to pollen produces breaks which are transmitted to only half of the resulting cells while, with roentgen rays similarly applied, all the subsequent cells are affected. It is as if the chromatin thread were already beginning to split and the roentgen rays affected both daughter strands while the ultraviolet radiation affected only one.

Neutrons have been shown to be highly effective in producing mutations. The work here is just beginning but it has already been demonstrated that the effect increases

with increasing dosage and that the influence is much more potent than that of roentgen rays if comparison be made in term of roentgens. The radiation is a mixture of gamma rays and fast neutrons and is not properly defined in roentgens. To avoid confusion the units as indicated by the r-meter have been termed pseudo-roentgens.

Short radio waves such as used in thermotherapy, and ultra-short waves have had no influence on mutation rate although they were applied in intensity high enough to kill most of the insects used.

Temperature differences at which the cultures have been reared change mutation rate and this according to van't Hoff's rule. The coefficient of change for 10° C. (Q_{10}) is about five, much higher than the ordinary values for a chemical change, between two and three. This follows because the rate of reaction of a single gene is very low, of the order of one change in one thousand to several hundreds of thousands of generations, very much lower than the rate for chemical reactions as observed in the laboratory.

Finally, various chemicals have been used in attempts to affect genes but results have been negative, probably because the chemicals cannot get at the genes without killing the protoplasm.*

* For discussion see page 279.

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THE BIOLOGY OF THE CANCER CELL*

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WHICH of the many processes commonly grouped under the term "growth" produce that growth which is called "cancer"? And wherein does it, or do they differ from the corresponding phases of normal growth? The answers to these questions couched in biological terms must be the points of departure for discussion of the biology of the cancer cell. From then on various radiating leads may be followed to see where they go, but always in terms of comparison with normal cells.

Arbitrarily, we may divide certain phases of growth into the processes of initiation, multiplication, differentiation and organization. Because of lack of time, this presentation must be confined to a brief comparison of them in normal and cancer protoplasm.

Cancer cells do not organize into definite structures, and this is the basis of our means of diagnosis. If they did organize, then a woman with cancer of the breast, instead of harboring a mass of cells which grow on and on in any and all directions and into no constant shape or structure, would develop another breast; a patient with carcinoma of the rectum, another rectum, and so on. At least another definite structure would be produced if cancer cells organized. Therefore, lack of organization must be compared to presence of organization as displayed by normal cells. But this is the very problem which is now rapidly coming to the fore in all of biology. In my opinion it is the core of biology. Why is it that the offspring of dogs are always dogs; of sea urchins, sea urchins; why do human mothers always produce some sort of sample of *Homo sapiens?* Why are livers shaped as they are; how is it that a giraffe's front leg is so built that it can be distinguished from a human arm by even the inexperienced in anatomy? And another most important question is, how is differential growth maintained, which means that in a given organism liver is not too large for heart which is not too small for kidneys, etc.? One of the most dramatic of all biological occurrences is that growth in all the meanings of this word takes place in relation to a Whole; all of the complicated processes head toward the completion and maintenance of a thoroughly integrated organism. This is organization. Its orderly progressions may be used as a starting point for the construction of a whole system of synthesis of knowledge and thought, i.e., a philosophy, something which is needed very badly at present. I risk the objections and even scorn of many by emphasizing this. Even some scientists are afraid of thinking, let alone speculating constructively to guide them in their experiments and application. But this is not the time for further development of this theme.

If, then, normal cells organize, it is obvious that the cells must be there to accomplish this. They get there by multiplication. And further, they differentiate into different kinds of cells before they organize. Thus:

1. Cells organize when they have multiplied and differentiated.

2. Cells differentiate when they have multiplied.

3. Cells multiply.

This is but a restatement of the well known autonomy of cells and their capacity to grow; the seedling splits the granite rock in which it embeds itself. From which it may well be that:

a. Cells multiply in order to differentiate and organize.

* Read in a Symposium on Growth at the Thirty-ninth Annual Meeting, American Roentgen Ray Society, Atlantic City, N. J., Sept. 20–23, 1938.

b. Cells differentiate because they have multiplied and in order to organize.

c. Cells organize because they have differentiated and multiplied.

This method of statement has a teleological flavor, but what of it if it leads to further useful concepts such as:

x. Cells cease multiplying because they have differentiated and organized.

y. Cells cease differentiating because they have organized.

It follows then that:

z. The natural inhibitors of cell multiplication are differentiation and organization, especially the latter.

Cancer cells continue multiplying, else they would not plague us as they do. They differentiate poorly and as stated, they do not organize at all. Can it be then that cancer cells continue multiplying *because* they do not differentiate properly and do not organize at all? If so, do they fail to organize because they cannot, or because the environment does not give them the proper building blocks to utilize for this function?

These two questions to me are fascinating, and I have not hesitated to adopt provisional answers as one of several central themes for the construction of plans for experiment. Indeed, I have used it as the basis of a definition of cancer to give force, direction and logic, not only to further exploration, but also to practical everyday experiences in the handling of cancer patients.

I believe, at present, that cancer cells do not organize because they cannot, and this is the reason they continue multiplying.

Since most organisms, including humans, are composed of protoplasm which has differentiated into cells, I will lay the emphasis on cellular terms, even though the old cellular doctrine has lost its force as a generality and become a special case, not only anatomically but also physiologically. For from the anatomic point of view, there are many large, perfectly competent organisms consisting of only one cell, and physiologically it may be said that one of the differentiations which protoplasm can undergo is that of dividing itself into cells. Even in human development, some tissues begin as syncytia and now and again a human tumor is encountered containing nuclei but no cell walls, i.e., a tumor as a syncytium. Thus the biology of tumor protoplasm must also consider the biology of plasmodia. Interesting though this is, again we must forego for a future session. Finally, it may be remarked that Mrs. Harvey, by centrifuging sea urchin eggs and removing their nuclei, has nevertheless observed cell division up to 500 or more cells and some differentiation without any nuclei at all. I have never encountered a tumor with no nuclei, but a normal analogy might be cited in the blue-green algae which have cell walls but no nuclei. Not even chromatin has been detected with certainty and yet they breed true; i.e., they differentiate and organize. All this is recited not so much to show how complicated the organization problem is, but to call attention to the fact that material for cancer study and comparison lies on every hand.

CELL MULTIPLICATION

The multiplication of cells means their increase in number; a single center of protoplasmic activity becomes two. Both normal and cancer cells multiply. Many studies are recorded in which the anatomic processes of division have been studied and the results have been nothing characteristic in the division process of malignancy.

In tissue culture the rate of division of cancer cells is at least as rapid and probably more so than in rapidly growing normal cells, e.g., connective tissue. In the animal body, cancer cells do not multiply as rapidly as normal cells can. This statement is usually challenged out of an old habit, but when it is remembered how quickly granulation tissue can grow, or how quickly a portion of liver may regenerate, we become thankful that a malignant growth does not reach the size of a human kidney in ten days or two weeks. And yet a liver can regenerate that rapidly.

Nor does increasing the rate of multiplication of normal cells lead to malignancy. When a normal chemical stimulus to division is used, e.g., sulfhydryl, there result more rapid differentiation and organization of the cells, but into normal parts or into "bigger and better" parts or whole organisms. Nor does altering timing relations lead to malignant growth. As an organism or a part is developing, or as regeneration, etc., takes place, the cells in the mass of living protoplasm are in different stages, some just multiplying, others differentiating, others organizing in the exquisitely timed sequence necessary for a perfectly formed structure to result. It is possible to interfere with this timing by, e.g., accelerating or retarding the multiplication phase, but no malignancy results. A misshapen part or at most a teratological structure results, but it organizes and stops growing.

Finally, it must be emphasized that cell cleavage *per se* is not the cause of differences between cells or tissues; it is not even always the first step in development, nor is it a factor in determining the kind of differentiation which a cell undergoes.

I do not think, therefore, that malignant growth is fundamentally a disease of cell division.

DIFFERENTIATION

When a cell differentiates it is transformed from the more general to the more specific. It turns into a unit capable of functioning as a part which helps maintain the organism as a Whole. In passing from an undifferentiated to a differentiated state its chemical composition is rearranged, a mesenchymal cell may become liver or bone; we no longer recognize the sacredness of the three germ layers. Many times definite and specific combinations are built to manufacture certain definite substances; thus, thyroxin in thyroid cells, saliva in salivary cells, and so on. Differentiation is always accompanied by organization, i.e., numbers of differentiated cells are gathered together in definite form to make a structure like a thyroid gland, salivary gland, etc.

The ability of a cell to differentiate, i.e., turn into something, is called its potency. An interesting and important question is how much of this potency of undifferentiated cells resides within the cell and how much is impressed upon it from without, i.e., from its environment. Again, there is no time to marshal evidence on this question and so we must be content merely to summarize. A large part of the potency which a cell can display is inherent within it, i.e., it is inherited as a part of the lineage from which it came. Certainly, species specificity is inherent, for embryo sea urchins and starfish develop into their respective animals even when living in the same environment.

A most important property of undifferentiated cells is that their potency is greater, both qualitatively and quantitatively, than is normally expressed. Thus, e.g., if the two cells of a divided sea urchin's ovum are separated, each will develop a perfectly competent new sea urchin. If this process is repeated, as many as eight sea urchins can develop from one ovum. The potency ordinarily displayed by a sea urchin's egg is one sea urchin, but it can give rise to at least eight. Its potency, therefore, is greater quantitatively than its normal realization.

There is one layer of living cells between the bark and wood of a tree, say, even one of the giant sequoias. Every now and then one of these cells divides; one daughter cell stays put, i.e., remains undifferentiated as what I call a "spare part" for future dividing. The other differentiates into either wood or bark as the occasion demands. This is an example of excess potency of the qualitative kind. Which of the potencies and how much a cell uses is determined by its environment in the broad sense of the word.

Another important consideration about differentiation is that a completely differentiated cell can no longer divide. There are, of course, stages to differentiation which are very difficult to measure, in fact have not been measured quantitatively as

yet, because of the inherent difficulties of the problem. It cannot be said, therefore, at what stage in differentiation a cell loses its ability to divide. We do not know of how much or what kinds of differentiation protoplasm is really capable; if we did, it would be possible to predict the future course of evolution more accurately than the wild guesses in which some indulge. Perhaps, however, it is when a cell enters into the last phase of differentiation, which it will undergo in the organism of which it is a part, that it loses its ability to divide. Differentiation, then, is the natural inhibitor of multiplication as stated in the preliminary remarks.

Finally, when a cell is differentiated, I believe on indirect but nevertheless good grounds without being able to bring certain proof, that it cannot retrace its steps and become undifferentiated again. A tissue can be de-differentiated in the sense of a more specific tissue being replaced with a less specific one—yes, but the replacement is not by the previously differentiated cells which de-differentiate. These cells perish and are replaced by new ones coming from undifferentiated cells—spare parts—which do not differentiate as far quantitatively, or the same qualitatively, as the tissue destroyed.

Granting, then, these two propositions and, as stated, there is proof of the former and I believe good evidence of the latter, viz., that (*a*) the potency of a cell is greater than its normal realization and (*b*) it cannot de-differentiate, a number of conclusions emerge in relation to malignancy. Among them are these:

Malignant growths arise from incompletely differentiated cells, i.e., "spare parts."

These "spare parts" are, of course, essential to survival of any organism, for from them come the cells to replace those worn out, e.g., the skin, blood cells; for physiological hyperplasias, for repair. Normally to repair a wound, cells multiply, differentiate and organize until repair is completed, i.e., organization is restored. If these "spare parts" multiply but do not differentiate properly and do not organize at all, we encounter what we call malignancy. If then potency is greater than realization, as it is, there should appear in malignancy many different pictures corresponding to no organization and perverted differentiation. This is exactly what we see and one of the horrors of it is the number of different names given to tumors and still being coined to the utter confusion of pathologist, roentgenologist and clinician alike. The essentials are: malignant growths arise from division—capable, therefore, incompletely differentiated cells, i.e., "spare parts," which having excess potency but not differentiating normally turn into pictures of infinite variety. We have dignified these varieties by separate names as though they were entities.

Of assistance in this naming process is the fact that there are degrees to the loss of differentiating ability displayed from tumor to tumor. This important fact has practical application. As a rule, tumors with less differentiated cells are more easily controlled by irradiation, but they grow more rapidly because they contain more cells of low differentiation which have not lost their power of division.

As stated, I believe at present that the reason cancer cells do not differentiate properly and do not organize at all is because they cannot. It will be impossible to consider all the reasons for this statement for it would require a considerable text on organization alone. One fact, however, may be mentioned. It is a common experience to see both normal and cancer cells multiplying in the very same environment, the former differentiating properly and attempting to organize, the latter not. Apparently the same building blocks are offered to both, but the cancer cells cannot use them. Some change has taken place inside of them. Since this change is transmitted from mother to daughter cells in much the same way and degree as the cancer grows, it is spoken of as "somatic mutation." Unfortunately, the word mutation is

subject to a variety of meanings and imputations. In the present connection my personal definition is "a transmissible, irreversible change in the composition of the cell involving its potencies of differentiation and organization." Lewis says the cancer cell is a new race of cells, which is about the same thing.

Numbers of different ways have been found to produce cancer experimentally. Among a long list of chemicals are tar, dibenzanthracene, methyl cholanthrene. To date, no one group or combination of atoms has been found to unite and correlate these.

Certain viruses produce cancer. So do roentgen rays. An important question still unsolved is whether cancer can be produced by any method in an animal which is not genetically predisposed. Certainly, guinea pigs are resistant; we have rubbed the skins of a number of guinea pigs three times a week with dibenzanthracene for five years until they died of old age without cancer appearing. On the other hand, certain strains of mice can be bred with less resistance to carcinogens. But these questions can be discussed no further.

In seeking a generalization it is at once apparent that lack of organization is a common factor in all malignant growths. Introducing some of the above considerations we may state provisionally and as a basis for exploration that a cell becomes cancerous when it loses its ability to pick up the requisite building blocks from the environment and build them up into the proper chemical composition and physical arrangement which responds to surrounding fields of influence and organismal forces. Words, and more words! yes, but chemical carcinogens, viruses, roentgen rays, chronic irritations produce cancer by changing the chemical and physical composition of division—capable cells. What are the chemical compositions of cells; what changes are undergone when a cell differentiates; what chemicals influence growth and development and what phase? I could go on indefinitely and ask questions which can be made subject to experimental attack, and that is the important fact of this discussion.

DEFINITION OF CANCER

Cancer is a mass of cells that arise from and continue to proliferate within an organism as a result of and in direct proportion to the extent of their internal qualitative differences from the other cells of the organism particularly with respect to the potencies of differentiation and organization.

DISCUSSION OF PAPERS BY DRS. HAMMETT, WHITING AND REIMANN

Dr. Stanley P. Reimann, Philadelphia. I do not want to say very much in discussion of these papers. I simply want to thank you for the opportunity of bringing a little bit of biological lore to your meeting because I feel, as you do, that the basis of our profession is biology and that if we know more biology we will be better doctors; that if we do anything in medicine which is contrary to the proper principles in biology, we are not practicing proper medicine. Therefore, I, for one, am very glad to bring these few random thoughts on the biological underneath of some of the things which perplex us in this particular growth problem of malignant disease; not that these things do not perplex us in normal growth too, for they do, but they are particularly perplexing in malignancy. I can see nothing better as an approach than to start from the biological side, whether from plants, from animals, from high or lowly organisms and then add to it as much chemistry as possible and as much physics as we can.

Dr. Whiting (closing). It seems to me that these various phases of the problem of malignancy come together very nicely. Dr. Reimann mentioned fundamental changes, internal changes in malignant growth, and it seems to me that those are really somatic mutations. Perhaps they are not, but we do not know enough about the chromosomes in cancer cells in malignant growth. We have in the fruit fly, *Drosophila*, a number of definite genetic factors which cause malignant disease and various tumors, and we know at what point, in what chromosome, these various factors are located. Some of the tumors developed are so-called benign tumors; others are malignant. There is one point, for example, in the sex chromosome

which causes a benign tumor. A tumor develops in the body cavity of the larva and sometimes it kills the animal, sometimes it does not, but it is usually benign because it happens to occur in certain places that are not vital; the animal does not die. It can go ahead and reproduce. That is a very definite change, a mutation in a very definite gene located at a definite point in the sex chromosome which causes this.

I have said that all of the cells of the body are of the same genetic constitution in the fruit fly. There are, however, certain exceptions. I believe that the tumor cells in the affected flies have changed; that is, something happened to a gene or chromosome so that it mutates. It has become unstabilized and therefore it can change at some point in development, and that point varies apparently according to chance. In the same stock, we get different conditions.

To come back to the matter of viruses, the viruses are said by some to be free genes, floating around loose. There is a good deal of evidence that there may be something to this idea, because of their rate of mutation or their rate of change under treatment with roentgen rays and so on; also, the size of the virus molecule, whatever that may be, is similar.

It seems to me, therefore, that a great many of these points are really coming together, the study of radiation effects and somatic mutations—of course, we do have somatic mutations; I showed some in my slides, where a certain portion of the chromosomes was knocked out by irradiation; that is, certain cells produced white eyes in a red-eyed fly, because white was recessive there. That is also true for bristles there. We have all sorts of changes that may be brought about in the body by treatment with radiation.

Of course, those are not cases of malignant growth but other cases may be; we may produce malignant growth by irradiation or we may knock it out so that the cells which would go ahead and multiply or proliferate are not able to do so because they have what a geneticist would call dominant lethal conditions, the same sort of thing or very similar to the thing we are able to produce in the sperm cell, so that the egg which is fertilized is thereby killed; an egg which would normally develop parthenogenetically. Other forms do not develop parthenogenetically. We cannot get any statistical evidence on these because we do not know whether or not the egg is fertilized. Here you know that it is fertilized if it dies; if it is not fertilized, then it does not die.

Dr. Rollin H. Stevens, Detroit. This discussion has been very stimulating. I may be getting to be rather an old man now because in my spare hours I have been trying to learn something about these "spare parts" and newer developments in different branches of science that enter into our knowledge of disease, particularly of carcinoma. We must keep abreast of the natural sciences. We should have much more of them in our future programs. It might be a good idea to have some of these essayists on the lecture series such as we have been having in the mornings, for it seems to me this newer knowledge is fundamental to our understanding of cancer.

I would like to offer a motion that we extend a vote of thanks to the gentlemen who have taken part in this program this afternoon. I think it has been a very fine part of our meeting here.

Dr. Alexander H. Pirie, Montreal, Canada. I would like to second that motion, and also to comment upon how this extremely scientific work is being used commercially. I little thought that my gardening, of which I am so fond, would come up in a meeting such as this. I have been using indolacetic acid to make my plants grow. I never thought I would hear about it here today. But it is becoming commercial, and I have seen some cuttings grow in a way that I never expected by using this acid, which I heard mentioned today by one of the speakers.

Dr. E. P. Pendergrass, Philadelphia. I would like to ask Dr. Reimann if, in closing the discussion, he would comment upon colchicine and whether that has any value as a therapeutic agent along with irradiation.

Dr. Reimann (closing). I was amazed when I first saw what colchicine does. It was shown to me by Dr. Ludford in England. All the cells stopped proliferating in a certain phase of multiplication and there they were, a perfectly gorgeous picture of mitosis.

Therefore, if the roentgen rays hit cells harder while they are in mitosis, it appears theoretically to be a good drug to give before roentgen treatment, because then there would be a great many more cells—division-capable cells, of course, for if they are not division-capable, they won't go into mitosis—there would be a great many more division-capable cells in mitosis at

a certain time. Then the dose of roentgen rays could be delivered. At what time? Well, experiments with mice—and note that they were not transplanted but spontaneous tumors—an important distinction, in spontaneous tumors of mice the maximum effect is found about four hours after colchicine is given to them in comparatively large doses.

We happened to be doing some biopsies and we gave some patients colchicine at different times before the piece of tissue was taken out. We dropped the tissue in the appropriate fixative and stained it in the appropriate way. We found, sure enough, that in a few patients it was possible to arrest many of the cells in mitosis at this particular phase. That was about four hours after the dose was given.

Unfortunately, in order to give a sufficient dose to stop every cell in mitosis, it is necessary to give too much colchicine for the comfort of the patient. On the other hand, we have given as high as 1/60 of a grain by mouth, and four hours later we have taken a piece of tissue, and many of the cells in mitosis were arrested in that particular phase. On the basis of that, I believe some roentgenologists have given colchicine and then delivered their roentgen-ray dosage.

It will take a long while, of course, to tell whether delivering it that way is better than delivering the dosage to the same kind of tumor without colchicine. Unfortunately, you cannot tell what would have happened if you had not given the drug. This is one of the fundamental difficulties with which medical men are always confronted. However, dosages as high as 1/60 of a grain can be given, and if it helps just a little bit to destroy some cells, certainly it is worth while using and trying, at least from the theoretical point of view.

The colchicine loses its effect after a period of ten to twelve hours in mice. I do not know how long it keeps its effect in humans because we have not pursued that to the extent of being able to say anything definite, but it keeps the cells there for a period of a number of hours at least, beginning about four hours after the dose is given. Then, after a while, when it lets go, the cells go on and multiply; the tumor keeps right on growing.

What happens to human tumors in respect to doubling chromosomes from colchicine and all the rest of that, I do not know. I sometimes get pieces of tumor and fix them in Flemming's solution or others and ask my friends, the cytologists, to look at the human chromosomes. They always look at me dismally and say, "That's an awful job, to look at human chromosomes," so I don't get very far with that. Maybe that is one of the reasons why I can't answer a few very definite questions which you may have in mind in relation to colchicine, questions which we ought to be able to answer but just cannot do so as yet.

THE AMERICAN JOURNAL OF ROENTGENOLOGY AND RADIUM THERAPY

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Forty-first Annual Meeting: Boston, Mass., October 1-4, 1940.

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Delegates to the Sixth International Congress of Radiology: Albert Soiland, Los Angeles, Calif., Delegate, Zoe A. Johnston, Pittsburgh, Pa., Alternate Delegate.

Twenty-fifth Annual Meeting: New York City, June 10-11, 1940.

EDITORIALS

TREATMENT OF OSTEOGENIC SARCOMA

OSTEOGENIC sarcoma is a dread disease and its treatment is fraught with considerable disappointment. Amputation is the treatment commonly urged for osteogenic sarcoma of an extremity and it has always been believed that the earlier the amputation was done the more hopeful would be the outcome of the case.

Recently Ferguson* has reviewed the first 400 cases of osteogenic sarcoma in the Registry of Bone Sarcoma of the American College of Surgeons, excluding those cases with inadequate data or where the diagnosis was seriously disputed. From an analysis of this group of cases he draws the conclusion that early amputation not only is not the best treatment but it actually tends to assure the death of the patient. "Early amputation" is interpreted by Ferguson as amputation within six months of the onset of symptoms.

In his analysis he classified survivors as patients living with no evidence of tumor at the last report more than five years after amputation and the last surgical treatment.

It is interesting to note that only 8 per cent survived early amputation, whereas 29 per cent survived later amputation. This survival difference, Ferguson says, cannot be explained by a lesser degree of inherent malignancy in patients having delayed amputation. This is evidenced by the fact that in patients in whom one or more pathologists thought that histological study indicated a lesser degree of malignancy 14 per cent survived early amputation, whereas 41 per cent survived when amputation was delayed. Singularly enough, early amputation was fatal even when malignancy may not have been great.

In another group of cases in whom one or more pathologists thought that the lesion might be of unusually high malignancy, only 4 per cent survived early amputation and 37 per cent survived when amputation was delayed.

In a given lesion of the extremity one might think that early amputation would be the proper treatment for osteogenic sarcoma and that the earlier the amputation, the better would be the results. Contrary to this, however, Ferguson found that amputations which were performed within the first six months after the onset of symptoms yielded the poorest results. In those patients where the extremity was amputated in the first month after the onset of symptoms none of the thirteen patients survived. With amputation in the second month one of twenty-five patients survived; with amputation performed in the third month, two of twenty-three patients survived and where the amputations were performed in the fourth, fifth and sixth months following the onset of symptoms eight of seventy-three patients survived.

In the face of such an analysis one can only draw the conclusion that "very early amputation is fatal."

A further study of the history of the patients brought forth the information that of the eleven patients that survived early amputation all were in the age period of from eleven to twenty, and all but one had lesions at the distal portion of the femur. Ferguson remarks that in this series a patient had practically no chance of survival following early amputation unless he was in the age period of from eleven to twenty and unless the disease was located in the distal portion of the femur.

It is the practice of some institutions to administer irradiation before amputation. Ferguson's study of this group of cases indi-

* Ferguson, A. B. Treatment of osteogenic sarcoma. *J. Bone & Joint Surg.*, Jan., 1940, *22*, 92–96.

cated that irradiation before amputation seemed to improve the results of early amputation but did not definitely affect the results of late amputation, and he also elicited the information that irradiation alone did not effect a cure in any case in this series of 400 cases. He did find, however, that excision before amputation appeared to be a useful treatment as his study showed that when excision preceded amputation 17 per cent survived early amputation and 29 per cent survived late amputation.

The results of early amputation and those of late amputation were not notably affected by any treatment except excision or irradiation before amputation nor were they notably affected by such incidents as biopsy, fracture, or incision and drainage.

If the results from early amputation are so poor, what method of treatment could be instituted to bring about better end-results? Frankly, Ferguson, says that if early amputation is wrong, the best way to treat the early case of osteogenic sarcoma of an extremity is at present unknown. But the results might be improved, he says, by delay of amputation, with irradiation during the period of delay, which should further improve the end-results, and excision might be used to advantage before amputation.

Exactly why delayed amputation offers a longer period of survival or cure is not quite clear. Ferguson advances a theory that in the early months of osteogenic sarcoma the growth is a rapid one and the disease does not consist solely of a local lesion but of a local lesion plus innumerable tumor cells circulating in the flowing blood. These free tumor cells apparently need some aid to enable them to leave the blood stream and locate where they grow. The shock attendant upon the amputation produces this aid in the migration of the tumor cells, but for some unknown reason minor operations such as biopsy, incision, curettage or excision do not offer the same aid. He therefore suggests that the time selected for amputation be done in a quiet period. This quiet period could be determined by the fact that there had been no sudden increase of pain or of size of the tumor for at least two months and that there was no recent weight loss and when the roentgenogram revealed no evidence of extension of the tumor or increase in the size of the soft tissue mass.

Immunity or resistance to the tumor is discussed and Ferguson refutes the idea that the better results of late amputation are due to this as exemplified by the results of excisions. It was found that early excisions yielded much better results than those performed more than six months after the onset of symptoms.

It is apparent that the proper treatment of osteogenic sarcoma of an extremity should be to find or to create a proper time for amputation and then to amputate. What are the factors that tend to create a proper time for amputation? Irradiation is useful, he says, in that it tends to reduce the more virile cells to a less virile state in which they are less apt to be able to form metastases in the lungs at the time of amputation. Excision is also useful. It was also found that when bone grafts were inserted at the site of excision of osteogenic sarcoma the development of recurrence was retarded, the bone grafts or chips filling in the space which otherwise would be occupied by blood clot or fibrin, media suitable for the growth of tumor cells.

The treatment which Ferguson advocates for osteogenic sarcoma of an extremity as a result of his analysis of the large group of cases is: (1) avoidance of early amputation; (2) delay of amputation; (3) irradiation before amputation; (4) irradiation, excision, and implantation of a bone graft or bone chips before amputation, with amputation following before recurrence becomes evident; (5) repetition of excision before amputation, if recurrence is evident before amputation has been done.

It can readily be seen from this analysis that the present treatment of osteogenic sarcoma is far from ideal and possibly as a result of this careful study a better or more universal form of therapy may be evolved in the treatment of what is now a rather hopeless condition.

GLENN R. FORD
1893–1939

DR. GLENN R. FORD of Endicott, N. Y., was born on July 1, 1893, at Cazenova, N. Y., and died on September 9, 1939. He was a graduate of the Fulton, N. Y., High School, and of Syracuse University in 1919. He interned at the Rochester General Hospital, and spent a year in the post-graduate study of radiology at the University of Pennsylvania in 1921–1922. He was engaged in private practice in Rochester, N. Y., in 1922 and 1923, and entered the Endicott Johnson Medical Service on March 15, 1923. He was a member of the Binghamton Academy of Medicine; Broome County Medical Society; Central New York X-ray Society; also a diplomate of the American Board of Radiology, and became a Fellow of the American College of Radiology, in 1939. He was also elected to membership in the American Roentgen Ray Society in 1939. Dr. Ford was in charge of the Department of Radiology at Ideal Hospital, Endicott, N. Y., and also at the Charles S. Wilson Memorial Hospital, Johnson City, N. Y. He was married, and is survived by his wife and one child.

RESOLUTIONS

WHEREAS On September 9, 1939 death unduly claimed our respected colleague, Dr. Glenn Ford and

WHEREAS From 1923 when he first engaged in practice in Endicott, N. Y. he rapidly gained eminence and proficiency in his chosen specialty of X-ray serving as active Roentgenologist at Ideal and Wilson Memorial Hospitals, 1927–1939 and,

WHEREAS The American Board of Radiology and the American Roentgen Ray Society honored him with membership during his brief years of practice and he served as Chief of Staff of Ideal Hospital 1938–1939 and,

WHEREAS Those who were associated with him and countless others who came in contact with him socially and professionally attest to his ability, gentlemanly bearing and sincere devotion to his specialty coupled with a loyalty deeply ingrained through several years of pleasant contacts,

BE IT THEREFORE RESOLVED, That the Broome County Medical Society wishes to express to the family of Dr. Glenn Ford its deep sense of loss of so promising a physician and,

BE IT THEREFORE RESOLVED, That a copy of these resolutions be sent to the family of Dr. Glenn Ford, a copy to the American Roentgen Ray Society, and a further copy spread on the minutes of the Broome County Medical Society.

It is with regret that the Journal announces the death of Aristide Busi, Professor of Radiology in the Atheneum of Rome, Founder and Emeritus Honorary Member of the Italian Society of Medical Radiology, which occurred in Rome on October 30, 1939.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer.

MEETINGS OF ROENTGEN SOCIETIES*

UNITED STATES OF AMERICA

AMERICAN ROENTGEN RAY SOCIETY
Secretary, Dr. C. B. Peirce, Royal Victoria Hospital, Montreal, Canada. Annual Meeting: Hotel Statler, Boston, Mass., Oct. 1-4, 1940.

AMERICAN COLLEGE OF RADIOLOGY
Secretary, Mac F. Cahal, 540 N. Michigan Ave., Chicago, Ill. Next Annual Meeting: Commodore Hotel, New York City, June 12, 1940.

SECTION ON RADIOLOGY, AMERICAN MEDICAL ASSOCIATION
Secretary, Dr. J. T. Murphy, 421 Michigan St., Toledo, Ohio. Annual meeting: New York City, June 10–14, 1940.

RADIOLOGICAL SOCIETY OF NORTH AMERICA
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting, 1940: To be announced.

RADIOLOGICAL SECTION, BALTIMORE CITY MEDICAL SOCIETY
Secretary, Dr. Walter L. Kilby, Baltimore. Meets third Tuesday each month, September to May.

RADIOLOGICAL SECTION, CONNECTICUT MEDICAL SOCIETY
Secretary, Dr. Max Climan, 242 Trumbull St., Hartford, Conn. Meets twice annually in May and September.

SECTION ON RADIOLOGY, ILLINOIS STATE MEDICAL SOCIETY
Secretary, Dr. H. W. Ackemann, 321 W. State St., Rockford, Ill. Next meeting Peoria, Ill., May 21–23, 1940.

RADIOLOGICAL SECTION, LOS ANGELES CO. MED. SOC.
Secretary, Dr. Wilbur Bailey, 2007 Wilshire Blvd., Los Angeles, Calif. Meets on second Wednesday of each month at County Society Building.

RADIOLOGICAL SECTION, SOUTHERN MEDICAL ASSOCIATION
Secretary, Dr. Roy G. Giles, Temple, Texas.

BROOKLYN ROENTGEN RAY SOCIETY
Secretary, Dr. L. J. Taormina, 1093 Gates Ave., Brooklyn, N. Y. Meets monthly on first Tuesday, October to April.

BUFFALO RADIOLOGICAL SOCIETY
Secretary-Treasurer, Dr. Joseph S. Gian-Franceschi, 610 Niagara St., Buffalo, N. Y. Meets second Monday of each month except during summer months, place of meeting selected by the host.

CHICAGO ROENTGEN SOCIETY
Secretary, Dr. C. J. Challenger, 3117 Logan Blvd. Meets second Thursday of each month October to May inclusive at the Hotel Sherman.

CINCINNATI RADIOLOGICAL SOCIETY
Secretary, Dr. J. E. McCarthy, 707 Race St., Cincinnati, Ohio. Meets third Tuesday of each month, October to May, inclusive.

CLEVELAND RADIOLOGICAL SOCIETY
Secretary, Dr. H. A. Mahrer, 10515 Carnegie Ave. Meets at 6:30 P.M. at Mid-Day Club rooms on fourth Monday each month, October to April, inclusive.

DENVER RADIOLOGICAL CLUB
Secretary, Dr. P. R. Weeks, 520 Republic Bldg., Denver, Colo. Meets third Friday of each month.

DETROIT ROENTGEN RAY AND RADIUM SOCIETY
Secretary, Dr. E. R. Witwer, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

FLORIDA STATE RADIOLOGICAL SOCIETY
Secretary, Dr. J. N. Moore, 210 Professional Bldg., Ocala, Florida. Meetings in May and November.

GEORGIA RADIOLOGICAL SOCIETY
Secretary, Dr. R. C. Pendergrass, Prather Clinic Bldg., Americus, Ga. Meets in November and at annual meeting of Medical Association of Georgia in the spring.

ILLINOIS RADIOLOGICAL SOCIETY
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meetings held quarterly, on the fourth Sunday of the month.

INDIANA ROENTGEN SOCIETY
Secretary, Dr. C. C. Taylor, 23 E. Ohio St., Indianapolis, Ind. Meeting held the second Sunday in May annually.

KENTUCKY RADIOLOGICAL SOCIETY
Secretary, Dr. J. C. Bell, 402 Heyburn Bldg., Louisville. Meets annually in Louisville on third Sunday afternoon in April.

LONG ISLAND RADIOLOGICAL SOCIETY
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:30 P.M.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS
Secretary, Dr. C. S. Davenport, St. Lawrence Hospital, Lansing. Three meetings a year, Fall, Winter, Spring.

MILWAUKEE ROENTGEN RAY SOCIETY
Secretary, Dr. I. I. Cowan, Mt. Sinai Hospital, Milwaukee, Wis. Meets monthly on first Friday at University Club.

MINNESOTA RADIOLOGICAL SOCIETY
Secretary, Dr. J. P. Medelman, 572 Lowry Medical Arts Bldg., St. Paul.

NEBRASKA RADIOLOGICAL SOCIETY
Secretary, Dr. D. A. Dowell, Medical Arts Bldg., Omaha, Nebr. Meets first Wednesday of each month, at 6 P.M., at either Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY
Secretary, Dr. A. O. Hampton, Massachusetts General Hospital, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

RADIOLOGICAL SOCIETY OF NEW JERSEY
Secretary, Dr. W. J. Marquis, 198 Clinton Ave, Newark. Meets annually at time and place of State Medical Society. Mid-year meetings at place designated by president.

NEW YORK ROENTGEN SOCIETY
Secretary, Dr. R. D. Duckworth, 170 Maple Ave., White Plains, N. Y. Meets monthly on third Monday, New York Academy of Medicine, at 8:00 P.M.

NORTH CAROLINA ROENTGEN RAY SOCIETY
Secretary, Dr. Major Fleming, Rocky Mount, N. C. Annual meeting at time and place of State Medical Society. Mid-year scientific meeting at place designated.

CENTRAL NEW YORK ROENTGEN RAY SOCIETY
Secretary, Dr. C. F. Potter, 820 S. Crouse Ave., Syracuse. Three meetings a year—January, May, November.

PACIFIC ROENTGEN CLUB
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

PENNSYLVANIA RADIOLOGICAL SOCIETY
Secretary, Dr. L. E. Wurster, 416 Pine St., Williamsport, Pa. Annual meeting, June, 1940, exact time and place to be decided.

PHILADELPHIA ROENTGEN RAY SOCIETY
Secretary, Dr. B. R. Young, Temple University Hospital. Meeting first Thursday of each month from October to May inclusive, at 8:15 P.M., in Thompson Hall, College of Physicians, 19 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY
Secretary, Dr. H. W. Jacox, 4800 Friendship Ave., Meetings held second Wednesday each month, 4:30 P.M., October to June at various hospitals.

ROCHESTER ROENTGEN RAY SOCIETY, ROCHESTER, N. Y.
Secretary, Dr. S. C. Davidson, 277 Alexander St., Meets on second Thursday from October to May, inclusive, 8 P.M., Rochester Academy of Medicine Building.

ST. LOUIS SOCIETY OF RADIOLOGISTS
Secretary, Dr. W. K. Mueller, University Club Bldg. Meets fourth Wednesday of October, January, March and May, at a place designated by the president.

SAN FRANCISCO RADIOLOGICAL SOCIETY
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco. Meets monthly on first Monday at 7:45 P.M., alternately at Toland Hall and Lane Hall.

* Secretaries of Societies not here listed are requested to send the necessary information to the Editor.

South Carolina X-Ray Society
Secretary, Dr. Hillyer Rudisill, Jr., Roper Hospital, Charleston. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. F. B. Bogart, 311 Medical Arts Bldg. Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. H. C. Harrell, 517 Pine St., Texarkana, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets every Thursday from 4:00–5:00 P.M., Room 301, Service Memorial Institute.

Virginia Radiological Society
Secretary, Dr. V. W. Archer, University Hospital, University, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. K. J. Holtz, American Bank Bldg., Seattle. Meets fourth Monday of each month at the College Club, Seattle.

Cuba

Sociedad Cubana de Radiologia y Fisioterapia
Secretary, Dr. Francisco Padron, Enrique, Villuendas 64, Havana, Cuba. Meets monthly in Havana.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Meets monthly on third Thursday, from November to June inclusive, at 8:15 P.M., 32 Welbeck St., London.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets on the third Friday of each month during the winter at 8:15 P.M. at the Royal Society of Medicine, 1, Wimpole St., London, W. 1.

Faculty of Radiologists
Secretary, Dr. Barbara M. Key, 32 Welbeck St., London, W.1, England.

Section of Radiology and Medical Electricity, Australasian Medical Congress
Secretary, Dr. H. M. Cutler, 139 Macquarie St., Sydney, New South Wales.

Radiological Section of the Victorian Branch of the British Medical Association
Secretary, Dr. Keith Hallam, St. George's Hospital, K.E.W., Melbourne, E. 4, Victoria, Australia. Meets monthly from March to Nov. incl. for scientific discussion.

Canadian Association of Radiologists
Secretary, Dr. A. C. Singleton, Medical Arts Bldg., Toronto, 5, Ontario.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext., Halifax, N.S.

Radiological Section, New Zealand British Medical Association
Secretary, Dr. Colin Anderson, Invercargill, New Zealand. Meets annually.

Continental Europe

Belgian Society of Roentgenology
Secretary, Dr. J. Boine, Avenue des Ailiés, 134, Louvain (Belgium).
Meets monthly on second Sunday at d'Egmonds Palace, Brussels, except in the summertime.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7, Madrid, Spain. Meets monthly in Madrid.

Société de Radiologie Médicale de France
Meets monthly on second Tuesday, except during months of August and September, 12 Rue de Seine, Paris.

Société Suisse de Radiologie (Schweizerische Röntgen-Gesellschaft)
Secretary for French language, Dr. A. Grosjean, La Chaux de Fonds.
Secretary for German language, Dr. Scheurer, Molzgasse, Biel. Meets annually in different cities.

Société Francaise d'Electrothérapie et de Radiologie Médicale
Meets monthly on fourth Tuesday, except during month of August and September, 12 Rue de Seine, Paris.

Association of German Roentgenologists and Radiologists in Czecho-Slovakia
Secretary, Dr. Walter Altschul, German University, Prague, II.52.

Deutsche Röntgen-Gesellschaft (Gesellschaft für Röntgenkunde und Strahlenforschung)
Meets annually in April, alternating one year in Berlin, one year in some other German city. Meets in addition every two years with the Gesellschaft deutscher Naturforscher und Aerzte.
Permanent Secretary, Professor Dr. Haenisch, Klopstockstrasse 10, Hamburg, Germany.

Süd- und Westdeutsche Röntgensellschaft
Meets annually in different cities.

Nord- und Ostdeutsche Röntgengesellschaft
Meets annually in different cities.

Dutch Society of Electrology and Roentgenology
Holds two meetings a year in Amsterdam, one in the Spring, and one in the fall.

Societa Italiana Radiologia Medica
Secretary, M. Ponzio, University of Turin, Prof. Turin

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banul Mărăcine, 30, S. I., Bucuresti, Roumania.
Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad, USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson, Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly on first Monday at 8 o'clock.

Polish Society of Radiology
Secretary, Dr. Jan Kochanowski, 45 Gornoslazka St., Warsaw. Meets annually.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. B. Krynski, 11 Zielna St.
Meets once a month except in the summertime.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association. Each of the following societies, with exception of the Denmark Society, meets every second month except in the summertime:

Society of Medical Radiology in Sweden
Meets in Stockholm.

Society of Medical Radiology in Norway
Meets in Oslo.

Society of Medical Radiology in Denmark
Secretary, Dr. G. Biering, Copenhagen.
Meets the second Wednesday of each month from October to July in Copenhagen, at 8 o'clock in the State Institute of Roentgenology.

Society of Medical Radiology in Finland
Meets in Helsingfors.

Vienna Roentgen Society
Meets first Wednesday of each month, at 6:30 P.M. at Zentral-Röntgen Institut des allgemeinen Krankenhauses Alserstrasse 4.

Orient

Japan X-Ray Association
c/o Orthopedic Surgery, Tokyo Imperial University. Meets annually in April.

Kinki Roentgen-Abend Society
Director, Dr. Prof. Taiga Saito, Ogawaoike Tyoto Japan. Meets bi-monthly on third Sunday.

BULLETIN OF THE INTER-SOCIETY COMMITTEE FOR RADIOLOGY

Points of Interest

The following communication was sent to the Inter-Society Committee *state representatives* on November 15:

Once there was a boy who cried, "Wolf!" so often when no wolf came that the men who heard him paid no attention. Then one day, the wolf came and the men were sorry they had not heeded the boy's warning.

For several years, radiologists have warned surgeons, internists, obstetricians, urologists, orthopedists, *et al.*, that hospitals would one day dominate all medicine if a few specialties were sacrificed to economic convenience. If hospitals could practice radiology, it has been said, they could likewise practice other specialties. If radiology is included as a hospital benefit in group hospitalization plans, there is nothing to prevent the inclusion later of other services.

Radiologists have appealed for help from their colleagues and warned of dangerous consequences to all medicine if such help were not forthcoming. Sometimes such help has not been forthcoming.

Well, here comes the wolf!

David B. Skillman is Chairman of the Trustee Section of the American Hospital Association. He is a hospital administrator from Easton, Pennsylvania. At the recent annual meeting of the American Hospital Association in Toronto, Canada, Mr. Skillman delivered himself of a paper on medical and hospital economics.

The following is quoted from a report which appeared in *Modern Medicine* for November, 1939:

"Salaries for Doctors.—A proposal that hospitals establish faculties of doctors with definite salaries has been forwarded as a means to combat socialized medicine. Mr. David B. Skillman, Chairman of the Trustee Section of the American Hospital Association, would fix the salaries starting at $1,800 to $2,000 a year for young, unmarried practitioners, and advancing to $10,000 or $12,000 for men of advanced standing.

"The hospitals would submit their bills according to a published scale of prices. The plan is merely an expansion of the group hospitalization plan to take in medicine, and would eliminate state, county, and federal support."

This to combat socialized medicine, says Mr. Skillman. Indeed! One might say also that Finland could have avoided invasion by the Soviets if she had asked for military occupation by the Nazis. Individual determination and freedom is sacrificed one way or the other.

* * * *

In its many and laudable activities for the protection and preservation of the private practice of medicine, the *Kansas State Medical Society* has never failed to apply its principles to all branches of the profession.

Recently, the Committee on Tuberculosis of the Kansas State Society discussed the question of consultation service in the interpretation of roentgenograms when such is desired by individual physicians. The following resolution was adopted:

1. That the committee believes the principles of the private practice of medicine should be followed in the handling of X-ray consultations.
2. That the Committee urges physicians who desire X-ray consultations on tuberculosis cases to utilize the services of the radiology specialists of the state.
3. That the radiologists of Kansas at a meeting held on January 15, 1939, agreed they would provide this service without charge to any patient who is deemed to be indigent by the attending physician, and that, therefore, no problem is presented in this connection.
4. That in the instances of X-ray consultations desired for non-indigent patients the Committee recommends that the services of a radiologist be utilized with the expectation of paying a fee for that service.

A fee of $2.50 has been recommended as the proper sum to charge for roentgen examinations in connection with tuberculosis in indigent patients. The fees for non-indigent patients are to be governed by the usual and customary charges in the community.

* * * *

Radiologists concerned about the ultimate destiny of the specialty of radiology in

the citadel of medicine should be interested in the following news letter from *Bucharest* which was published in the *Journal of the American Medical Association* almost two years ago:

Regulation of the Title X-Ray Specialist

"The position of the X-ray specialists has undergone an unfavorable change in recent years. The number of X-ray installations is growing by leaps and bounds, owing to the fact that the peasants falsely believe that only physicians who own an X-ray apparatus can establish a good diagnosis. General practitioners, almost without exception, own X-ray sets, even in villages where there is no electricity and where they have to work their sets with gasoline motors. This situation affects badly the X-ray specialist, who receives his patients from the general practitioners. Another drawback for the X-ray specialist is that the general practitioner shows on his name plate that he possesses an X-ray apparatus, so when a patient drops in, seeing the name plate, for a roentgenogram of a dislocated wrist, he does not refer the patient to the X-ray specialist but keeps the case for himself. The X-ray specialists held a conference to find a remedy for this situation. The result was that the Supreme Health Council made the following resolutions:

"1. Physicians who have an X-ray apparatus in their office with the aim to establish diagnoses and control the progress of certain diseases on their own patients must not call themselves specialists in radiology and they are not entitled to display on their name plates and on their prescriptions that they have an X-ray apparatus or that they deal with radiologic treatment, and they are not entitled to issue X-ray reports.

"2. Only such physicians can be acknowledged as X-ray specialists as those who have gained their diploma in Rumanian universities and received a license to call themselves 'specialist in radiology.'

"3. Physicians who in 1930 had been in roentgenologic practice for five years receive the title of specialist simply on the verification of the city medical officer of health."

* * * *

The Council of the *Ohio State Medical Association* discussed the status of group hospitalization insurance in that state during a recent meeting. The following statement of policy was adopted and copies were transmitted to all county medical societies:

Statement of Policy

It is essential that the medical profession take an active interest in all proposals or programs affecting the care of the sick. Leadership must be assumed by state and local medical societies.

Realizing that there is increasing public interest in programs to provide hospitalization on a voluntary insurance basis and anticipating the expansion of group hospitalization programs in Ohio under the provisions of enabling legislation enacted at the recent session of the Ohio General Assembly, the Council of the Ohio State Medical Association believes that all county medical societies should give the question of group hospitalization immediate and earnest consideration.

Inasmuch as hospital service programs are administered through local units, the responsibility for considering medical questions which may be involved rests with the individual county medical society. The Council suggests that county medical societies in counties where hospital service programs are now in operation and county medical societies where such programs are under consideration carefully evaluate the contracts being sold, or which are being formulated by hospital service associations. Special attention should be given to the coverage provisions of such contracts.

The Council recommends that county medical societies use the following principle as a guide in evaluating contracts and in conferences with hospital service association representatives:

The subscriber's contract should exclude all medical services. Contract facilities should be limited exclusively to hospital facilities such as bed, board, operating room, medicines, surgical dressings, general nursing care, and services of intern and resident staff in assisting the subscriber's attending physician.

If the above principle is complied with by all local hospital service associations in formulating a schedule of benefits, the result would be a certain uniformity of policy and procedure

throughout the state, efficiency in administration, and absence of misunderstanding.

The medical profession of Ohio believes that group hospitalization programs, in the hands of reputable and efficient administrators, are of definite public benefit, providing such programs are limited to hospital services and do not include medical services, which inclusion would have an undesirable effect on the practice of medical specialties in hospitals and on the quality of the service rendered. Group hospitalization plans operated in accordance with the above principle should have the active cooperation of the medical societies in the localities in which they operate.

* * * *

The following is from the *New York Medical Week:*

Danger Ahead

A local judge recently imposed a fifteen-dollar fine, for passing a red light, on a motorist who admitted illiteracy. At the same time he criticized severely the system which permits drivers who cannot read or write to operate cars. No matter how competently a motorist handles his machine, he is not a safe driver if he cannot read certain warning signs.

In technical fields allied to medicine there is a parallel to this situation. Many registered physiotherapists consider themselves qualified to practice medicine because they can operate their apparatus, although they are completely unable to read danger signals in a patient's condition or make a diagnosis. It is a sad and well-known fact that physicians often employ commercial X-ray and clinical laboratories whose technicians do not know how to interpret the signs set before them.

Whether in driving or medical practice, a certain amount of knowledge is necessary besides mastery of an inanimate machine. It is doubtful, however, whether the illiterate motorist is nearly as dangerous as the lay technician who takes to the medical road without being able to read warning signs.

* * * *

Dr. E. H. Skinner and *Dr. F. F. Borzell* have been selected to serve on the Executive Board of the National Physician's Committee for the Extension of Medical Service. The formation of the Committee was stimulated by earlier activities opposing governmental regimentation of medicine carried on by publisher Frank Gannett's National Committee to Uphold Constitutional Government. The present Committee, however, has no connection with the Gannett Committee, nor with the American Medical Association. The stated objectives of the Committee are to cooperate "with lay and medical institutions and groups, interested in the preservation of national health, and to make more generally known the achievements and to safeguard the independence of American medicine."

BOOK REVIEWS

Books sent for review are acknowledged under: Books Received. This must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers as space permits.

Outline of Roentgen Diagnosis: An Orientation in the Basic Principles of Diagnosis by the Roentgen Method. By Leo G. Rigler, B.S., M.B., M.D., Professor of Radiology, University of Minnesota, Minneapolis, Minnesota. Atlas edition. Cloth. Price, $6.50. Pp. 212, with 254 illustrations shown in 227 figures, presented in drawings and reproductions of roentgenograms. Philadelphia: J. B. Lippincott Company, 1938. (Also furnished in a Student Edition, 212 pages, $3.00.)

This textbook of Rigler's is exactly what it purports itself to be, an outline and not a complete textbook. The method of presentation is that of a summary or of an outline for lectures and there are few words wasted in pictorial description. In the ideal textbook (yet to be written) all possible conditions and every conceivable variation must be described accurately and pictured perfectly both by description and by photographic copying of the highest quality. Rigler's Outline considers only the more common conditions, giving them their proper relative emphasis, it is true, but leaving out many essentials.

His presentation is precise and concise, at times to the point of too much brevity. The material is very well arranged and subdivided, easy to skim through and already summarized, ideal for a harried medical student, but not for the graduate intending to enter roentgenology, or for the roentgenologist. Of particular value to the medical student are the considerations of roentgenological methods, technical procedures, normal anatomy and possible errors, which precede most of the main anatomically arranged chapters. Of even more value are the summaries at the end of each section, where Rigler gives his honest opinion as to the "value of x-ray examination" in that particular condition or part. These "values" are in the main correct, reasonable and not-too-enthusiastic estimates of the usefulness of the roentgen method, a matter which is often very uncertain in the average student's mind.

The illustrations are good in two particulars, poor in others. (The book has two editions, one with the illustrations or "Atlas" and the other one without this very necessary feature). The good points are that all of the roentgenograms are presented in their proper value of blacks and whites, i.e., negatives, thus avoiding the additional confusion to students of having to interpret some roentgenograms as positives, others as negatives. Another good point is the excellent use of outline or line drawings, in the section on the heart particularly, further avoiding confusion. Some of the defects in illustrating are that text and figure are separated, all of the illustrations being printed on different paper and bound together at the back of the book. This adds confusion, requiring frequent turning of pages, loss of continuity and mental exasperation in trying to combine text and pictorial images. The reproduction of roentgenograms is fairly good, but the "original technique" of illustrating most of the bone lesions is sadly lacking in clarity and in detail. The artist has given all of the bones a peculiar stippled appearance which may be the way they look to her, but to the informed reader it would seem that all of the cases suffered from an advanced degree of splenic anemia, and it must be confusing to the average student.

The book is well set up mechanically, running to 212 pages including the index, and 122 unnumbered pages of illustrations, with the figures or drawings all on the right hand page and descriptive text on the opposite page, with only the common conditions pictured in the 227 illustrations. The book could have been smaller as there is an unusually wide margin for the text, 3.5 cm. at the sides and 5.5 cm. at the bottoms of the pages. The type is clear and easy to read, the headings are uniform and well spaced, and the left marginal offsets correspond accurately to the subheadings. There are surprisingly few typographical errors for a first edition, but there are several colloquialisms which might be eliminated, such as "slow growing," "operated stomach," "perinephritic abscess" instead of the more grammatically correct "slowly growing," "postoperative stomach" and "perinephric abscess."

On the whole, this book is a good one for medical students—an "Orientation in the Basic Principles of Diagnosis by the Roentgen Method," as the author's subtitle puts it, and particularly valuable if combined with the actual demonstration of roentgenograms in more detail and variety than is done in the "Atlas" portion of the book. But as a text for graduate study, for reference, or for consultation, it is decidedly incomplete.

M. C. S.

Roentgen Technique. By Clyde McNeill, M.D. Cloth. Price $5.00. Pp. 315, with 268 illustrations. Springfield, Illinois: Charles C Thomas, 1939.

The author's purpose has been to produce a practical reference book of roentgen technique and this has been carried out in a very excellent manner. For each technical procedure he has reproduced a photograph illustrating the position together with either a finished roentgenogram or a line drawing from the roentgenogram, diagrammatically illustrating the desired end-result. On the opposite page to these he gives the technical factors, a description of the position, the purpose of exposure and/or the salient points bearing thereon, together with a bibliography in certain cases where a special, more detailed knowledge may be desired of the procedure by the reader.

The book is divided into four parts. The first deals with the head, the second with the extremities, the third part with the trunk, and the fourth part deals with exposure techniques and methods of preparation of opaque media, etc. In the first part the author has a series of drawings indicating the angle of projections in the various head positions. These are very comprehensive. Following these he proceeds to explain the various routine positions for roentgenography of the head. The routine encephalographic positions are shown. Special mention should be made of the section on dental roentgenography and foreign body localization in the eye. Measurement of the pineal body position is also discussed. The second part, dealing with the extremities, has a section on bone development, anatomical variations and accessory bones, which precedes the routine explanation of positions. The section on the trunk, after dealing with the skeletal portion, outlines the procedures for roentgenography of the chest, abdomen, and the special examinations where opaque material is used. Pelvic mensuration is also discussed as well as tomography and kymography.

In his preface, the author points out that relatively little space was devoted to practical exposure technique since this is the portion that most quickly becomes obsolete.

Obviously in a work which attempts to be as comprehensive as this, minor omissions occur which are not to be considered of too much importance. Often various individual laboratories have their own favorite methods which might be missed by one too critical. It is to be assumed that the reader realizes that often the standard positions cannot be accomplished because of the condition of the patient, particularly in fracture work. For example, one is reminded, when reading the portion on roentgenography of the hip and upper femur, that the standard positions here which are described are often very difficult to obtain because they are usually used for fracture of the hip. If fracture is not present, then the extremity can usually be manipulated into the position described by Hickey some years ago, which gives as good a lateral view of the femoral neck as any position. This position is not mentioned.

Further, nothing is said about routine work with the portable apparatus at the home or on the hospital ward.

Again the necessity for making several exposures of the spine in the anteroposterior position to compensate for curvatures which might be present is not stressed. These are, however, not very serious omissions.

Perhaps a little too much stress has been laid on pelvimetry and cephalometry since it is now generally recognized that measurements *per se* are of little value.

McNeill has done an admirable work. His efforts represent one of the best monographs of this kind that has been added to the literature in recent years. The construction of the volume comes up to the usual high standard of the publisher.

Paul C. Swenson

Clinical Roentgen Therapy. Edited by Ernst A. Pohle, M.D., Ph.D., F.A.C.R., Professor of Radiology, Chairman, Department of Radiology and Physical Therapy, in the University of Wisconsin, Madison, Wisconsin. Foreword by George W. Holmes, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roent-

genology in Harvard Medical School, Boston, Mass. Cloth. Price $10.00. Pp. 819, with 199 illustrations. Philadelphia: Lea & Febiger, 1938.

A glance at the index of this book shows that it begins with "Abortion produced by roentgen rays" and ends with "Xanthomatosis." This simple fact indicates that the book covers a wide field. It also indicates the wisdom of the editor in choosing a number of well known contributors, inasmuch as a single individual obviously lacks the background of training and experience to cover the entire field adequately. By the same token the reviewer is likewise handicapped in his appraisal of all of the subject matter.

One might well question the wisdom of the editor in divorcing "Clinical Roentgen Therapy" from "Theoretical Principles of Roentgen Therapy." The two subjects are treated in separate volumes without anything in the respective titles to indicate that they are in reality companion works. The former is not complete without the latter. Taken together the two give a well rounded exposition of the present status of roentgen therapy which should prove a great boon to teachers, students and practitioners in this highly important field. The latter, particularly, not only owe it to themselves and their patients to use the books liberally, but they also owe it to radiology as a whole in order that the editor and contributors may be encouraged to issue such future editions as may be required to keep the work abreast of future developments.

Thomas A. Groover

Radiation Therapy: Its Use in the Treatment of Benign and Malignant Conditions. By Ira I. Kaplan, B.Sc., M.D., Clinical Professor of Surgery, New York University Medical College; Director, Radiation Therapy Department, Bellevue Hospital, New York; Director Division of Cancer, Department Hospitals, City of New York, etc. Cloth. Price, $10.00. Pp. 558, with 198 illustrations. New York: Oxford University Press, 1937.

Kaplan's enormous clinical experience is reflected in this excellent book. The use and methods of radiation therapy, as found in the busy and highly specialized cancer clinics, or in the general and private practice of radiology are ably presented.

Beginning with a brief historical development of radiation therapy and ending with two unusual chapters: nursing care of patients with malignant conditions, and suggestions as to the organization and equipment of a radiation therapy department. The book clearly and concisely covers the vast field of therapeutic radiology.

One unusual feature is the chapter on the use of electrosurgical currents, a much neglected but essential modality in the treatment of many diseases.

The body is systematically divided into regions, and due consideration is given both benign and malignant lesions. One or several elective techniques using roentgen rays or radium are carefully and clearly presented so that the reader has no difficulty in following them. The individual requirement of the patients or the available equipment determines the exact type of therapy utilized

There are many good illustrations. The radiologist will find the book a useful and valuable text.

R. Rhett Rathbone

Disability Evaluation. Principles of Treatment of Compensable Injuries. By Earl D. McBride, B.S., M.D., F.A.C.S., Assistant Professor in Orthopedic Surgery, University of Oklahoma School of Medicine; Attending Orthopedic Surgeon to St. Anthony's Hospital; Associate Orthopedic Surgeon to Wesley Hospital, etc. Second edition revised. Cloth. Price, $8.00. Pp. 623, with 374 illustrations. Philadelphia: J. B. Lippincott Co., 1938.

This comprehensive 623 page volume is written as a reference for the physician who finds it necessary to participate in legal controversies dealing with compensation for industrial injuries. The provisions of workmen's compensation laws as they are applied in each province of Canada and each state of the United States are given in detail in the first portion of the book. An attempt is then made to standardize and evaluate the various types of disability with mathematical accuracy, and the methods of examination on which the evaluation depends are described for each portion of the body.

The loss of function and resulting disability following partial or total ankylosis are considered separately for each joint in the skeleton and another large section deals with the temporary or prolonged interference with useful

activity resulting from the proper or improper healing of all well known fractures. The industrial back receives its share of attention and separate chapters are devoted to nerve injuries, amputations, head injuries, injuries of the eye and ear, burns and hernia.

Proper methods of treatment are illustrated in each instance and frequent reference is made to the importance of roentgen studies as a protection against malpractice suits. Unfortunately roentgenograms are referred to as "x-ray pictures" in many of the charts copied from exhibits prepared by the American Medical Association but on the whole the illustrations are well chosen to illustrate the points made in the text. Although the determination of disability is a clinical rather than a roentgenological problem any roentgenologist who examines industrial injury cases can find in this treatise much valuable information not included in the curricula of most medical schools.

Charles L. Martin

Vol. 43, No. 2

DEPARTMENT OF TECHNIQUE

Department Editor: Robert B. Taft, M.D., B.S., M.A., 105 Rutledge Ave., Charleston, S. C.

AN INTRANASAL CONE FOR THE CHAOUL APPARATUS

By LESTER HOLLANDER, M.D., *and* JOSEPH M. SHELTON, M.D.
From the Pittsburgh Skin and Cancer Foundation
PITTSBURGH, PENNSYLVANIA

IN THE past two years we have been using the Chaoul apparatus in the treatment of intracavitary neoplasms. During this time we have treated 5 patients suffering from intranasal malignant disease, including 2 of melanocarcinoma.

The ordinary cones are much too large to permit introduction into the nasal cavity, thus it was necessary to devise an auxiliary cone for this purpose.

This cone consists of a piece of nickel-brass metal tubing 1 cm. in outside diameter, having a wall thickness of 1 mm. This tubing is 3 cm. in length and is imbedded in a molded lead base attached to a short sleeve which fits into the aperture of a standard 3 cm. cone. The over-all length of the cone is 4.25 cm., increasing the target-skin distance to 7 cm. This increased distance and the narrowed aperture decreases the roentgen output to 20–35 r per minute, thus necessitating a daily exposure of fifteen to twenty minutes to reach our usual dose of 400 to 500 r daily.

In all cases there has been a marked regression in the local growth although the 2 melanomas terminated fatally. In spite of the fact that the radiation is directed "blindly" to a certain extent, our rhinologist reports that we have been able to obtain satisfactory local results without extensive damage to the adjacent normal mucosa.

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ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

ROENTGEN AND RADIUM THERAPY

HERNAMAN-JOHNSON, F. The after-care of patients suffering from breast cancer. *Brit. J. Radiol.*, May, 1938, *11*, 297–310.

A large proportion of all cases of breast cancer will be dead within five years. Metastases in microscopic form are already present in a large proportion of breast cases when the primary tumor is first recognized. The five year survival statistics have been greatly improved by postoperative radiation treatment, but the ultimate mortality rate from cancer of the breast has not been affected.

Very great advances have occurred in the matter of alleviating the lot of the breast cancer patient. We must seek to prolong to the uttermost the lives of these patients, provided we can make these lives useful and happy. The majority of patients suffering from cancer of the breast should be told the truth at the first suitable moment after microscopic examination has confirmed the diagnosis. The expression "after-care" means the care of the patient after the primary growth has been dealt with.

Efficient supervision of all breast cases from the time of the operation onwards is best carried out in any given area by one man rather than by fifty. As the physician in charge of radiotherapeutics is the person who will inevitably be called upon to deal with them when they go wrong, logic demands that he should have the supervision of them from the comr .ence-ment. Systematic after-care can best be carried out by the creation of a special clinic, to which all patients are sent as soon as possible after operation. The author established an after-care clinic at the Croydon General Hospital three years before presenting this article and, of the 33 patients registered three years ago, 19 patients are still attending the clinic. The advantages to be gained by the establishment of an after-care clinic are summarized. One of the advantages is the lessons to be learned from the necessarily closer study of each patient.

For purely prophylactic treatment in good risk operable cases, heavy dosage carried to a

point where healthy tissues may be damaged is not justified. When there is localized recurrence, heavy dosage over a strictly localized area is valuable as a palliative. For practical purposes, breast cancer in its later stages must be regarded and treated as a general disease.

Attempts have been made for many years to find some drug which would be selectively destructive to malignant cells. The alternative is to find some way of stimulating tissue resistance. Todd, of Bristol, believes that the resistance mechanism is to be found in the reticuloendothelial system. He further believes that if certain compounds of selenium be introduced into the circulation, the element finds its way into this system, and can thereafter be activated by means of roentgen rays, and that by this means tissue resistance to cancerous invasion can be stimulated. The author cites several cases which showed marked improvement following Todd's method of treatment. He believes, however, that the results are too uncertain to warrant the use of this method in routine hospital practice.

Mention is made of the use of biochemical tests as a guide to treatment and prognosis in cancer of the breast. The test employed has been the differential sedimentation test. In known cases of the disease it has a value in indicating the kind of fight which the patient is putting up against the disease.

Local recurrence in the skin or in the axilla can be cured or held in check by irradiation. Invasion of the supraclavicular glands may also be confined to this site by heavy roentgen-ray dosage. Swelling of the arm which does not improve with heavy doses of roentgen radiation to the axilla may be relieved by surgery.

Radiotherapeutics, if it is to progress, must not ally itself exclusively with surgery and physics, but must look to medicine for guidance and more particularly to those branches of it which are known as endocrinology and biochemistry.—*S. G. Henderson.*

Sosman, Merrill C. The roentgen therapy of pituitary adenomas. *J. Am. M. Ass.*, Sept. 30, 1939, *113*, 1282–1285.

There are three important fundamental principles to be established before consideration of the results of roentgen therapy alone. We must judge our results by the patient's restoration to health, a return to a normal mode of living and, particularly in the chromophobe type of adenoma, by restoration of vision. With modern accurate penetrating radiation one can and does give larger and more accurately measured total doses, spreading treatment over a longer period and using more portals, and can justifiably expect from present indications a greater effect on the tumor. Pituitary adenomas are extremely variable in their rate and direction of growth, and their effect on health and vision and, like all adenomas of endocrine glands, are liable to spontaneous remissions. It might be more valuable to analyze and compare failure rather than to consider only good results.

Seven of 8 patients with the chromophobe type of adenoma received marked benefits from the irradiation, both as to restoration of vision and as to return of the patient to normal living. The duration of improvement in the cases has lasted from three to five years, with no recurrences so far. Failures occur in patients with advanced extensive lesions, either invasive in bone or with large intracranial extensions. Failures may also occur in cases in which the tumor has been pressing on the optic nerves or chiasm so long that it has produced atrophy of the fibers. Cystic tumors, which formed 17 per cent of Cushing's 260 chromophobe tumors, are said not to respond to irradiation.

The dangers from or following irradiation are real but infrequent. Henderson found in one case extensive adhesions between the adenoma and the chiasm, which prevented a satisfactory surgical removal. He assumed the adhesions to be due to extensive irradiation elsewhere for more than a year before operation. Sosman has seen an acute hemorrhagic cyst develop after a fairly heavy single roentgen treatment for recurrence after operation. Cataract formation is a definite possibility after heavy (and perhaps careless) irradiation. Experiments lead one to believe that the nervous tissue of adults will stand a dosage up to 6,000 roentgens in any one area. One should keep below this dose, therefore, to avoid injury to the vessels and subsequent fibrosis, gliosis or necrosis. While roentgen therapy is being tried, the failure promptly to remove the pressure on the optic chiasm may possibly result, with unsatisfactory responses, in a change from temporary relievable blindness to permanent optic atrophy due to degeneration of the nerve fibers. Acidophil tumors and acromegaly respond more readily to irradiation than the chromophobe type. The majority of them can best be treated by irradiation,

and they are much more liable to spontaneous remissions and waves of activity and inactivity. These tumors grow slowly and the eventual result is in doubt for many years. The most distressing symptom of nearly all the patients irradiated was headache, and this was definitely improved or entirely relieved in 90 per cent of 28 cases.—*S. G. Henderson.*

BARTSCH, H., and WACHNER, G. Herzgefässschädigungen und ihre Prophylaxe bei protrahiert-fraktioniert bestrahlten Tumoren der oberen Luft- und Speisewege. (Cardiovascular injuries and their prophylaxis in protracted fractional irradiated tumors of the upper air and food passages.) *Strahlentherapie*, 1938, *62*, 339–342.

While cardiovascular injuries have been repeatedly demonstrated experimentally following intensive irradiations, the data regarding such injuries on humans are meager. Coutard and Lavedan were the first to call attention to this phenomenon. They have observed numerous patients with symptoms of dyspnea, shortness of breath, and muscular weakness. Physically they were able to demonstrate tachycardia, a fall of blood pressure, a decrease of the blood pressure amplitude, intensification of heart murmurs, etc. In benign cases these phenomena disappeared after a few weeks, while in severe cases the improvement was delayed and not infrequently death occurred.

Parade was able to demonstrate, on the basis of a study of 2 cases of mitral stenosis, the development of severe cardiac disturbances as a result of roentgen irradiation which led to auricular fibrillation and absolute ventricular arrhythmia. One of these cases was treated for a tumor of the thorax and the other for carcinoma of the uterus; in the first case one had to deal with a direct and in the second with an indirect effect of the irradiation.

Schinz and Zuppinger have called attention to the danger or threat to the circulation or to the body as a whole during the Coutard method of irradiation of tumors of the upper air and food passages. Eight of the 30 cases irradiated for carcinoma of the pyriform sinus died at the end of irradiation from pulmonary and circulatory complications. In one case a latent decompensation was transformed following the irradiation into a manifest decompensation. Also Lambadaridis was able to demonstrate untoward effects on the circulation under the influence of Coutard's method of irradiation. These effects were expressed in the form of a fall of the blood pressure, a decrease of the amplitude, the appearance of extrasystoles and myocarditic disturbances. Some authors are of the opinion that the presence of a poor heart is a contraindication to Coutard's method of irradiation. Mayer reported the development of an acute cardiac weakness following irradiation.

These authors observed cardiovascular injuries in patients subjected to the protracted fractional method of irradiation of the tumors of the upper air and food passages. In 47 cases with predominantly carcinoma and occasionally sarcoma of the epi- and hypopharynx and of the larynx, with or without regional glandular metastasis, the irradiation was carried out as follows:

Daily the right and left cervical field, including the supraclavicular fossa and in cases of epipharynx tumors, also the cheeks, of an area of 50 to 150 sq. cm. were alternately irradiated, one field in the forenoon and the other field in the afternoon. The irradiation was given in the course of four weeks. The individual dose varied from 100 to 200 r with a zinc filter of 1 mm. and 40 cm. focus-skin distance. The total dose was on the average 7,500 r surface dose.

Before and after each irradiation an orthodiagram, pulse frequency, blood study and electrocardiogram were obtained. In a large number of cases a lowering of the blood pressure combined with a decrease of the blood pressure amplitude, an increase of pulse frequency, as well as changes in the electrocardiogram, were found pointing to a disturbance in the process of contraction, expressed in the electrocardiogram in the form of the intercallated part and a flattening of the T-wave. In individual cases disturbances in rhythm were also observed. The changes in the electrocardiogram were most pronounced towards the end of the irradiation but some of them were apparently capable of regression.

To verify these findings, a series of experiments was carried out on rabbits with and without exposure of the heart, and following the irradiation the changes in the heart were studied histologically. In many of these cases the histologic changes simulated those found in severe cases of toxic myocarditis. These authors are of the opinion that these changes in the heart are apparently the result of a decomposition of proteins and the changes appearing

in the electrocardiogram are interpreted by these authors as the result of the direct effect of the proteins on the myocardium; they believe that this effect is also responsible for the fall of blood pressure and the tachycardia. These authors are of the opinion that in a predominant number of cases treated in the above given manner the treatment is followed by an injury to the myocardium. In consideration of these findings, these authors recommend a prophylactic cardiac and circulatory treatment before the irradiation in order to prevent the possibility or danger of a cardiac or circulatory insufficiency. The so-called cardiac prophylaxis must not only be limited to measures of a general nature, but actually requires medicamentous treatment. They recommend digitalization even for a perfectly sufficient heart in order to prevent possible collapse following the roentgen treatment. In the clinic of these authors the prophylactic digitalization is carried out as follows:

Three days each week the patient is given a small dose of digitalis three times daily; in many instances the digitalis is given in the form of a liquid in amounts of 10 to 15 drops per dose An attempt is also made to improve the peripheral circulation by the prophylactic administration of caffein and similar substances (veritol, sympatol).

A comparison of the results obtained in two groups of cases, those treated prior to the roentgen therapy and those non-treated, has revealed the absolute value of this prophylactic treatment. Among the 20 cases treated in the above manner, only in one a fall of blood pressure of about 30 mm. Hg occurred, while in the remaining 19 cases the lowering of the blood pressure did not exceed 10 mm. Hg.; in 78 per cent of the non-treated cases symptoms of peripheral circulatory weakness appeared which came to manifestation in the form of a fall of blood pressure up to 65 mm. Hg. No change in the pulse frequency was observed in the treated cases while such a change was observed in 70 per cent of the non-treated cases. The work is concluded with the emphasis on the necessity of a corresponding prophylactic cardiac and circulatory therapy prior to the Coutard irradiation.—*A. S. Schwartzman.*

Weissig, Heinrich. Die Röntgentherapie der Erkrankungen des kindlichen lymphatischen Rachenringes. (Roentgen therapy of diseases of the lymphatic pharyngeal ring of children.) *Strahlentherapie*, 1938, *62*, 480–496.

One hundred and thirteen of the 120 children irradiated because of hyperplasia of the tonsils could be followed up and the results obtained were as follows:

Children with pure hyperplastic tonsils presenting no signs of inflammation or no signs of a catarrhal affection responded best to the treatment (62.5 per cent cured and 25–28 per cent improved). Of the hyperplasia in exudative diathesis only 37.5 per cent were cured and only 37.5 per cent were improved, therefore 75 per cent were favorably influenced. Children with fibrous indurated tonsils resulting from repeated severe throat infections do not respond as well. In those where irradiation was employed 44.4 per cent were cured and 30 per cent were improved. Children who had a previous history of scarlet fever responded especially poorly to the radiation therapy. Of these only 10 per cent were cured and 20 per cent improved. In cases of chronic recurrent angina and pronounced fibrous induration of the tonsils, surgery is preferably indicated.—*A. S. Schwartzman.*

Negru, D. Die Röntgenbehandlung der Basedowschen Krankheit. (Roentgen treatment of Basedow's disease.) *Strahlentherapie*, 1938, *62*, 450–479.

The beginning of roentgen treatment of Basedow's disease dates back to 1902. It was the first internal disease in which roentgen treatment was employed so that it was the first disease in which deep roentgen therapy was used. Nevertheless even at present there is no uniformity of opinion regarding the indication of this method of treatment in relation to surgical treatment; similarly there is no uniformity of view regarding the technique to be employed. According to some authors, many small doses at long intervals of time are recommended while according to others, large roentgen-ray doses at shorter intervals of time seem preferable. The subject of roentgen treatment of Basedow's disease was extensively studied by the author in the course of the last fifteen years during which time 428 patients were treated. Of these 428 patients treated, 295 could be followed up for a given length of time. On the basis of the results obtained

from these extensive studies, the author comes to the following conclusions: Roentgen treatment of Basedow's disease must be a functional therapy. Its purpose is to control the neuroendocrine disturbance in equilibrium which is represented by this disease. The functional disturbance in general seems to have as a material substrate a very labile biochemical construction which is changed and normalized by the roentgen rays irrespective in what direction the disturbance has occurred. This would explain the good results obtained from the same therapeutic agent in so different and frequently antagonistic conditions. It appears that there exists a definite difference in radiosensitiveness between the pathologic and normal biochemical processes whereby the former are considerably more radiosensitive. Because of the above it is more difficult to change the normal than the pathologic function of a cell. A selective process takes place which is comparable with that of the normal and the tumor cells in the destructive cytocaustic therapy.

The usual dose must not exceed $\frac{1}{3}$ skin erythema dose per sitting. Two to three irradiations of the same field with a pause of about one week between the sittings are suggested. The thymus gland must be irradiated but not more than with $\frac{1}{3}$ S.E.D. in one sitting. Depending on the volume of the struma the rays employed may be either hard or of medium hardness. No material difference is obtained from the use of a filter of 4 mm. aluminum or of 0.5 mm. of copper plus 4 mm. of aluminum. At least three series of treatments given in the course of four months are necessary in order to change the final effect of the treatment. The condition may be looked upon as cured when an absolute and permanent normalization of the pulse frequency, of the basal metabolism and of the body weight and a complete restoration of the working ability have been attained. The roentgen therapy produces no injury to the skin or to the larynx nor adhesions of the thyroid gland if correct and purely functional doses have been employed. A systematic control of the basal metabolism protects against myxedema which is an extremely rare and easily curable complication. The indications of roentgen therapy of Basedow's disease are very wide. Since roentgen therapy is a harmless method, it is to be preferred in all cases where definite contraindications do not exist. The most important contraindications are: strumata with symptoms of compression, a suspicion of a malignant degeneration, toxic adenoma which from the very beginning gives rise to severe toxic symptoms. In cases where irradiation of the thyroid gland and thymus remains ineffective, roentgen treatment of other glands of internal secretion should be tried (suprarenals, hypophysis, ovaries). If even this remains ineffective an operation is indicated. Severe cases represent no contraindication to roentgen therapy. The roentgen therapy must be instituted as soon as the basal metabolism decreases to plus 10 per cent. Roentgen therapy gives in about 40 per cent of all cases total or permanent cures. In nearly 80 per cent of all cases cures or improvements are obtained. Recurrences occur in about 10 per cent of the cases.—*A. S. Schwartzman.*

NEWMAN, WILLIAM W., and GARLAND, L. HENRY. The non-surgical treatment of hyperthyroidism complicating heart disease. *Surg., Gynec. & Obst.*, Nov., 1938, *67*, 632–639.

A combination of iodine and roentgen therapy for hyperthyroidism will result in 60 per cent of cures based on the disappearance of symptoms, economic restitution, a lowering of the basal metabolic rate to plus 10 or below, the pulse rate to 80 or below, and a gain of weight to near the former average. In another 28 per cent there is marked improvement so that there will be satisfactory results in over 80 per cent of cases. There is no direct mortality or complication, the patient is ambulatory, the effect is relatively rapid, and if the treatment fails surgery can always be employed. Its value for those who refuse surgery is obvious whatever the reason.

Data to support the above statements is given by the authors as sufficient to recommend this form of treatment though not in all cases necessarily the best. Their evidence is very convincing.

Medium or high voltage therapy is used with moderate filtration over a single anterior neck field. The trachea is protected by a narrow strip of lead rubber; 150–200 r, measured in air, is given every second or third day up to a total dosage of approximately 2,000 r. Iodine in the form of Lugol's solution is given three times a day (5–10 drops) from the start for amelioration of the symptoms until the irradiation effect has been produced in from three to six weeks.—*P. C. Swenson.*

Breitländer, K. Röntgentherapie des Ulcus callosum ventriculi und Ulcus pepticum jejuni postoperativum penetrans. (Roentgen therapy of callous ventricular ulcer and postoperative penetrating peptic jejunal ulcer.) *Strahlentherapie*, 1938, *62*, 331–338.

The author discusses a certain method of roentgen irradiation of chronic gastric ulcer (situated on the lesser curvature) and postoperative peptic jejunal ulcer. The technique of irradiation is basically as follows:

A sum total of 1,000 to 1,500 r surface dose is given depending on the course of the individual sittings, each of 100 r/o given every other day, 40 cm. focus-skin distance, 4.5 r/m, 180 kv. This method of treatment was employed only on chronic cases some of which gave a history of ulcer of years' duration and in each case, including the severe ones, the treatment was carried out under ambulant conditions. This represents the essential preference of this method since in a predominant number of cases the patients were able to follow their occupations. With the exception of the occasional administration of a dose of papaverin and anasesthesin-belladonna powder, no other treatment was given. Depending on the case, the ulcers disappeared from two, four to six weeks after the beginning of treatment. The patients were observed clinically up to two years and 90 per cent of them remained free of symptoms during this time. Altogether 48 cases were observed in this manner, 2 of which had a postoperative jejunal peptic ulcer. This method of treatment is not unpleasant to the patients, it is without any danger and is inexpensive. This author is of the opinion that the protraction and fractionization is decisive for the results obtained. He further believes that the roentgen method of treatment of jejunal peptic ulcer is definitely preferable to other methods, especially to surgical methods of treatment and he is convinced that in chronic peptic ulcer of the lesser curvature as well as in postoperative jejunal peptic ulcer good permanent results are obtainable by this method of treatment in a large percentage of cases. The basic point of the problem is essentially the question of dosage and it would be very desirable to consider this problem more thoroughly.—*A. S. Schwartzman.*

Todd, T. F. Rectal ulceration following irradiation treatment of carcinoma of the cervix uteri. *Surg., Gynec. & Obst.*, Nov., 1938, *67*, 617–631.

Ulceration of the rectum following radiation treatment of carcinoma of the rectum is given the name of "pseudo carcinoma" because of its resemblance to carcinoma on digital examination. Two types are described, one restricted to the rectal wall and the other involving mainly the perirectal tissues, producing a rather tumor-like perirectal induration. Biopsy may be necessary to rule out persistent or recurrent carcinoma. The etiology is essentially one of overdosage in the vaginal vault and a lengthy discussion of prophylactic measures is given; fixation of position of the radium applicators, checking of their position by roentgen ray, reduction of the dose in cases of retroversion and the use of the knee chest position during the period of irradiation.

The histology of the two types of lesions suggests a common feature of vascular occlusion probably due to thrombosis of the smaller branches of the hemorrhoidal vessels. This eventually brings about infarction and ulceration. Treatment of the ulcerations and their complications is discussed in detail.—*P. C. Swenson.*

MISCELLANEOUS

Glauner, R. Vegetatives Nervensystem und Röntgenstrahlen. (The vegetative nervous system and roentgen rays.) *Strahlentherapie*, 1938, *62*, 1–72.

A study of the clinical observations and experimental results reported in the literature reveals that only in rare cases is a definite proof of an actual influence of the vegetative nervous system by roentgen rays available. It appears that the utilization of roentgen rays in the treatment of the vegetative nervous system is still in its early beginning stages so that data of this type must be critically evaluated. A further study of the data reported in the literature indicates that the autonomous nervous system can be influenced by roentgen rays and hypotheses may be presented which would explain the mechanism of action of the radiation effect. Many local points of influence may be differentiated. Principally the following come under consideration: (1) the influence on the autonomous nerve endings of the skin, especially the skin capillaries; (2) the influence on the pre- or post-ganglionic nerve strands;

(3) the influence on the ganglion; (4) the influence on the suprarenals, and (5) the influence on the vegetative centers of the brain.

In regard to the influence on the nerve fibers it may be stated that such an influence has as yet not been proved and can hardly be considered. A paralysis of the peripheral medullated nerves can be obtained only from the use of extremely high doses of roentgen rays. The results obtained from the experiments carried out on non-medullated autonomous nerves are not conclusive and do not definitely show that they are sensitive to roentgen rays even though on the basis of their general physiological behavior it may be assumed that the non-medullated nerves are more sensitive to roentgen rays than the medullated nerves. In spite of that, however, even for the non-medullated nerve fibers roentgen doses are necessary which could hardly be considered therapeutically. This path of influence on the nervous system must therefore at present be discarded.

Histologic changes in the suprarenals can be obtained only from the use of very large doses. At this point it may be mentioned that even after a direct irradiation of the suprarenals no effect on the blood pressure is demonstrable when the skin is not irradiated at the same time. The effect of irradiation of the suprarenals comes to clinical manifestation only in the cases when a simultaneous irradiation of the paravertebral ganglia is carried out.

The relations are entirely different in regard to irradiation of the vegetative brain centers. Here the effect of the irradiation is unquestionable even though the results are not uniform. It must always be remembered, however, that late injuries may occur and consequently extreme care must be used in irradiations of this type.

Suzuki demonstrated the great sensitiveness of ganglia to roentgen rays. It has been more or less definitely shown that the cholin liberated during the roentgen irradiation plays the essential rôle in the results obtained from the irradiation. This author substantiates the hypothesis which, however, still needs experimental proof, that the cholin liberated by the roentgen irradiation influences the process of conduction of stimuli at the synapse into the ganglia, therefore, at the point of transition of the preganglionic fibers into the ganglionic cell.

At present it cannot be stated whether this influence is of an inhibitory or accelerating type.

On the basis of the existing data, this author expresses the view that the autonomous nerve endings and the points of transition of the preganglionic fibers into the post-ganglionic fibers into the ganglion change their irritability probably as a result of a cholin or a cholin-like substance liberated through the irradiation and that these changes are centripetally conducted in the sense of an increased or decreased irritability and come to manifestation as distant effects in other regions supplied by the vegetative nervous system while at the point of application of the roentgen rays only the local radiation effects are demonstrable.—*A. S. Schwartzman.*

Wüst. Untersuchungen über den Wert des Röntgen-Schichtverfahrens für die Diagnostik des Hals-, Nasen- und Ohrenarztes. (Investigations concerning the value of the roentgen layer technique for the otorhinolaryngologist.) *Fortschr. a. d. Geb. d. Röntgenstrahlen*, June, 1939, *59*, 509–551.

This is a long paper from the Charité in Berlin dealing with the experiences with the roentgen layer technique. The first part is concerned with a technical comparison of the two methods. One instrument is the planigraph, manufactured by Siemens according to the principle of Ziedses des Plantes, and the other the tomograph from the firm Sanitas. In the planigraph there is a sinus curve excursion of both the tube and the film while with the tomograph the motion is confined to the tube. It was found possible to cut a much thinner layer with the tomograph than with the planigraph; the planigraph, however, produced a more complete obliteration of the other layers. The method for studying skulls and sinuses is described and illustrated with particular attention to malignant tumors of the antra. If one may judge from the reproductions, the results are not impressive. One figure, however, shows an anteroposterior view of the larynx with the soft tissue detail brought out with great clarity.

One section deals with the comparative value of the conventional film, a film overexposed using the Potter-Bucky diaphragm, and the roentgen layer method in the study of the bronchial tree and especially for the identification of small foreign bodies of low density. The experiments were carried out on dogs and the

results seem to show a decided superiority of the layer technique. This also proved to be true in one clinical case where a bone fragment was lodged in a right main bronchus surrounded by dense lymph gland shadows.—*W. A. Evans, Jr.*

Birkelo, C. C., and Brosius, W. L. Roentgen visualization of pulmonary arterial circulation in autopsy material. *Radiology*, Sept., 1938, *31*, 261–292.

A method of studying the vascular alteration in the lung as the result of disease is described. The thoracic contents were removed *en masse*, preserving the same degree of lung collapse that was present before death as shown by the ante-mortem roentgenograms. The pulmonary artery was severed at the pulmonary ring and the heart and aorta dissected free from the lung. Then radiopaque material was injected into the pulmonary artery under constant manometric control. Roentgenograms were made of the inflated lungs before and after injection. The lungs were then deflated and re-injected with a fixing solution and later sectioned.

This is a preliminary report of the method and early observation. At present it seems probable that pulmonary tuberculosis causes a marked decrease in pulmonary arterial circulation in the portion of the lung involved and that this impairment is proportionate to the degree and stage of the tuberculous involvement and that it is permanent. They found that collapse measures decrease the total volume of pulmonary arterial circulation in proportion to the degree of collapse, but the circulation returns to normal when the lung re-expands.

There are a number of excellent illustrations of this work.—*J. H. Harris.*

Reinhard, M. C. A note on the use of clinical dosage meters using a thimble ionization chamber. *Radiology*, 1939, *32*, 282–283.

The author calls attention to: (1) The existence of a shadow cast when a thimble ionization chamber with a metal chamber tube is placed in the radiation beam either between the filter and the skin or directly on the skin. This shadow causes a definite decrease in the intensity of the roentgen-ray beam. (2) The variations in intensity when the thimble ionization chamber is placed in the center or at the periphery of the radiation area. The difference may amount to 20 per cent. (3) The variation in intensity with the degree of submergence of the chamber on the skin surface. This may amount to a difference of 12 per cent.—*J. H. Harris.*

Blair, Harry C. The alternation of blood supply as a cause for normal calcification of bone. *Surg., Gynec. & Obst.*, Oct., 1938, *67*, 413–423.

The author attempts by a correlation of certain clinical observations and theoretical considerations, to present a rather reasonable theory that normal calcification of bone is maintained by alternating ischemia and hyperemia. This same mechanism aids in the treatment of fractures. He feels that he has sufficient evidence to establish the idea that this variation in the blood flow to a given part of the skeleton is produced by the contraction and relaxation of muscles. The entire article must be read to appreciate the author's viewpoint for a short abstract cannot include all of the important theoretical considerations. However, it is important to bring out that if the theory is correct, then the clinical applications are very important, i.e. that heat and massage are contraindicated in recent fractures since they produce hyperemia and thus abnormal mobilization of calcium from the bone. Heat should be used only to help absorb calcium as in the case of calcification in a bursa. On the other hand, contrast baths and the use of alternating suction and pressure would be indicated. In fractures of the femoral neck, where because of the age of the patient the blood supply at best is poor, ischemia might actually help in the precipitation of bone salts if the other factors which tend to produce the opposite effect could be eliminated. This calls for very rigid anatomical fixation, however. Further, fixation of the wrist in fractures of the navicular should theoretically be done without preventing the use of the hand in order to facilitate healing here.—*P. C. Swenson.*

Meltzer, H., and Kühtz, E. H. Über den Einfluss der Röntgenbestrahlung auf das anorganische Gewebegerüst der Haut. (The influence of roentgen irradiation on the inorganic tissue framework of the skin.) *Strahlentherapie*, 1938, *62*, 406–424.

An attempt was made by the authors to determine whether under the influence of roent-

gen irradiation of the healthy skin any changes in the irradiated region occur in the salt content of the inorganic tissue framework, what is the nature of these changes, how soon after the irradiation do they appear and what differences are observed following a single and following a fractional irradiation.

At first a series of preliminary experiments was carried out which revealed that no differences whatsoever could be demonstrated in black and albino normal rabbits following roentgen irradiation with 220, 825 and 1,100 r. In the microscopically stained preparation any significant irradiation effect was not demonstrable. On the other hand, the reaction to the irradiation was clear cut in the charred preparation. For further study irradiation with a dose of 220 r appeared to be sufficient.

A single roentgen irradiation of the skin of the back of rabbits with 825 r was found to produce regularly definite changes in the inorganic salt content of the irradiated skin region. The changes came to manifestation in the epithelial and in the connective tissue parts. An increased salt content is already demonstrable seven hours after the irradiation. It reaches its highest point about thirty-one hours after the irradiation after which it begins to decrease during the following two to six days. After the seventh day, however, there regularly occurs an increase in the salt content which again reaches its highest point at about the twelfth day.

One has to deal here, therefore, with a biphasic reaction. It appears to be highly independent of clinical and histologic tinctorial parallel manifestations. The first phase of the salt increase corresponds somewhat to the early erythema and the second phase to the main erythema.

The increase and decrease does not affect all types of salts uniformly (reference is had to soluble and insoluble magnesium and phosphate salts). The relationship between the soluble salts and insoluble calcium salts apparently follows a given law during the course of the irradiation reaction. The authors believe that there is no other available method which would permit one to determine as exactly as the method under consideration the age of a roentgen reaction in the experiment.

Also following a fractional roentgen irradiation of the normal skin of rabbits with 825 r there is demonstrable a biphasic reaction but here the reaction is not as clear cut.—*A. S. Schwartzman.*